Multiple chemical sensitivity

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INTRODUCTION

Multiple chemical sensitivity (MCS) is a complex, multi-symptom, multi-system multi-organ illness that is induced by exposure to a wide variety of toxic environmental insults. It is often co-morbid with other overlapping syndromes and evokes a similar range of symptoms (Table 50.1).1–5

WHAT’S IN A NAME?

MCS goes under many names and overlaps with many other syndromes and conditions (see Table 50.1). The most frequently used terms recognize that chemicals and the environment are understood by the affected people to be associated with their disabling illnesses. Among the overlapping syndromes are disorders, diseases and misdiagnoses that any competent physician would be expected to identify, for example coeliac disease, carbon monoxide poisoning and hypothyroidism.

Other descriptors are drawn from particular locations, for example ‘Gulf War syndrome’ (GWS) from the first Gulf War (1990–91) and ‘new buildings syndrome’ with new furnishings. Occupations such as carpet-fitting, commercial flying and cabin crew, and shepherding are associated with the same constellation of symptoms. Other descriptors indicate the comprehensive nature of the illness and try to place it within known clinical conditions such as allergy. More specific terms seek to identify the mechanism of the illness (e.g. toxicant-induced loss of tolerance, TILT) or cause of the illness (e.g. systemic candidiasis). An interesting inclusion in the list is electromagnetic sensitivity; this often follows chemical exposure but can be a primary event.6,7

The bewildering number and origins of so many names reflects the problems of grappling with such a complex illness and trying to understand it in order to effectively diagnose and treat patients who have it.

The World Health Organization (WHO) classifies MCS under chapters S00–T98 – injury, poisoning and certain other consequences of external causes, specifically at T66–78 – other unspecified effects of external causes and T78.4 – allergy, unspecified; hypersensitivity not otherwise specified (NOS), idiosyncracy NOS. Among the exposures specifically listed are pesticides of various chemical types, fungicides and rodenticides, although the important chemicals polychlorinated biphenyls (PCBs) are not included (Table 50.2).8

This confusion is reflected in the prolonged and sometimes acrimonious debate that surrounds MCS and involves clinicians, patients and patient support groups, and demands for recognition from governments, the chemical, pharmaceutical and insurance industries, and regulatory authorities in many countries.

DEFINITION AND DIAGNOSTIC CRITERIA

Definition

The 1999 consensus is widely accepted and defines MCS as follows:9

- A chronic condition
- With symptoms that recur reproducibly
- In response to low levels of exposure
- To multiple unrelated chemicals
- Improves or resolves when incitants are removed
- Symptoms occur in multiple organ systems.

The major symptoms of MCS are summarized in Table 50.1, but a more extensive list is given in Table 50.3. Objective clinical signs have been identified in a wide variety of tissues and clinical systems in MCS (Box 50.1).

Diagnosis

Diagnosis should be made in the light of the above criteria. A comprehensive paper by Heuser emphasizes the need for the following:10

- A very thorough history
- A thorough physical examination, with special attention to the skin, blood pressure (orthostatic hypotension), movement and coordination
The use of appropriate clinical, laboratory and psychological tests.

Single-proton-emission computed tomography (SPECT), positron-emission tomography (PET), magnetic resonance imaging (MRI)\(^1\) and quantitative electroencephalography (qEEG) all provide details of any abnormal lack of function in the central nervous system. Magnetic resonance spectroscopy (MRS) also provides a powerful tool that has identified brain damage in veterans of the first Gulf War.\(^1\) Current perception threshold studies are especially important in investigating the peripheral nervous system, as they assess the small but important C-fibres (see below). Autonomic function needs to be assessed with regard to temperature, perspiration, vascular tone, heart rate, smooth muscle tone and other functions. The eyes are important, since dry eye syndrome is common in MCS. Ear, nose and throat complaints are also common and need to be investigated fully, as nasal and pulmonary passages are frequently damaged or dysfunctional. Gastrointestinal problems occur regularly, with malabsorption and weight loss. Liver function tests are valuable, while low salivary immunoglobulin A (IgA) levels often indicate an impaired mucosal defence mechanism. Kidneys and the urinary tract may be

<table>
<thead>
<tr>
<th>Aspects of environmental sensitivities</th>
<th>Commonly overlapping conditions</th>
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<tbody>
<tr>
<td>State of heightened reactivity to the environment</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Total allergy syndrome</td>
<td>Myalgic encephalomyelitis (ME), chronic fatigue syndrome</td>
</tr>
<tr>
<td>Universal allergy</td>
<td>Postviral fatigue syndrome</td>
</tr>
<tr>
<td>Toxicant-induced loss of tolerance (TILT)</td>
<td>Post-infectious neuromyasthenia</td>
</tr>
<tr>
<td>Multiple chemical sensitivity(ies) (MCS)</td>
<td>Yuppie flu</td>
</tr>
<tr>
<td>Multiple chemical hypersensitivity(ies)</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Chemical intolerance(s)</td>
<td>Migraine</td>
</tr>
<tr>
<td>Chemical acquired immunodeficiency syndrome (AIDS)</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Gulf War illness/syndrome (GW/S)</td>
<td>Allergies</td>
</tr>
<tr>
<td>Idiopathic environmental intolerance (EI)</td>
<td>Rhinitis</td>
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<tr>
<td>Environmental illness (EI)</td>
<td>Asthma</td>
</tr>
<tr>
<td>Environmental irritant syndrome</td>
<td>Food intolerance syndrome</td>
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<tr>
<td>Chemical injury/allergy</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Toxic injury</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Tight building syndrome</td>
<td>Major depression</td>
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<tr>
<td>Sick building syndrome</td>
<td>Anxiety or panic disorder</td>
</tr>
<tr>
<td>Twentieth-century disease</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Chemically induced illness</td>
<td>Aerotoxic syndrome</td>
</tr>
<tr>
<td>Chemical hypersensitivity syndrome</td>
<td>Organophosphate poisoning</td>
</tr>
<tr>
<td>Chemophobia</td>
<td>Sheep-dipper’s flu</td>
</tr>
<tr>
<td>Electromagnetic (hyper)sensitivities/intolerance</td>
<td>Disorders of porphyrin metabolism</td>
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<tr>
<td>Toxic carpet syndrome</td>
<td>Carbon monoxide poisoning</td>
</tr>
<tr>
<td>Systemic candidiasis</td>
<td></td>
</tr>
<tr>
<td>Multiple sensory sensitivity syndrome (MUSES)</td>
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</tbody>
</table>
MCS is increasingly recognized by legal and medical systems. It was first officially recognized in Germany and described, using the WHO’s ICD, as ICD-10-SGB-V, November 2000, under the code T78.4, ‘allergy, otherwise not specified’.16 Reports from Australia17 and Denmark18 have also been published. The Australian report includes a literature assessment, evidence from 22 witnesses, and 167 written submissions from Australia and overseas. It makes a recommendation for classification of MCS under its own

International recognition of MCS

MCS is increasingly recognized by legal and medical systems. It was first officially recognized in Germany and described, using the WHO’s ICD, as ICD-10-SGB-V, November 2000, under the code T78.4, ‘allergy, otherwise not specified’.16 Reports from Australia17 and Denmark18 have also been published. The Australian report includes a literature assessment, evidence from 22 witnesses, and 167 written submissions from Australia and overseas. It makes a recommendation for classification of MCS under its own

Nutrient status & utilisation must also be checked e.g. lowered Zn or B-vits can give depression. Some psychotic not psychosomatic i.e. physical nutritional cause. Chemical toxicity depletes these nutrients.
modification of the WHO codes as ICD-10-AM. The Danish report is more limited, drawing largely on a published review assessing the situation in the UK.19

In North America, MCS is widely recognized. In the USA, official recognition takes the form of reports from the Department of Justice, the Department of Housing and Urban Development, and the Department of Education, which accept MCS as a legitimate condition for their purposes. Medical resistance to MCS has begun to evaporate among the American College of Physicians.20 The American Medical Association and American Lung Association and Environmental Protection Agency state that “Claimants should not be dismissed as psychogenic and a thorough workup is essential ...” Large population surveys report 16–33 per cent of people as being sensitive to everyday chemicals.

In 1998, 25 US federal and 28 US state authorities were listed and summaries of medical and legal/compensation papers and cases provided. Canada has recognized MCS in ten state authorities21 and has published a major review of the evidence linking its recognition to human rights.22

In contrast, official sources in the UK have been resistant to any recognition of chemical sensitivity. The British Society for Allergy, Environmental and Nutritional Medicine (BSAENM; now the British Society for Ecological Medicine, BSEM) has published substantial evidence in recognition of MCS as an organic illness that can be diagnosed and treated effectively.23,24 Although MCS does not fit comfortably into current views on allergy, the Royal College of Physicians’ report Allergy: The Unmet Need records a huge increase in allergy in the UK.25 Currently one in three in the UK has some form of allergy, a total of 18 million people; of these, some 3 million have severe allergies. The Royal Commission on Environmental Pollution identified the need for a proper understanding of the health effects of novel chemicals used widely and distributed ubiquitously in the environment.26 A further report by the Royal Commission endorsed the validity of GWS, myalgic encephalomyelitis (ME; chronic fatigue syndrome, CFS) and MCS in its appendices.27 The Research Advisory Committee on Gulf War Veterans’ Illnesses from the USA summarized epidemiological studies indicating that 28–32 per cent of veterans from the first Gulf War are now ill with symptoms, including MCS.27

Veterans of the first Gulf War represent large cohorts of fit, young, male military personnel from the USA (n = 697,000) and the UK (n = 53,000) who were exposed to a wide variety of biological and chemical toxins.28 Such large numbers of personnel allow considerable statistical analysis of their illnesses (GWS). There is extensive evidence of damage to the central, autonomic and peripheral nervous systems, to the cardiovascular system, and to other organs and bodily systems, and there is evidence of birth defects in some offspring.

In Sweden, electrosensitivity is officially recognized but is seen as a condition rather than a disease.

### Prevalence of MCS and Estimated Costs in the USA

The confusion and lack of uniformity in trying to assess the prevalence of MCS in various communities makes any figures open to questioning; however, various large population surveys report 16–33 per cent of people being sensitive to everyday chemicals, with the best estimates coming from studies and reports in the USA (Table 50.4).29

<table>
<thead>
<tr>
<th>Reference</th>
<th>% with MCS</th>
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<tbody>
<tr>
<td>Bell et al.31</td>
<td>15</td>
</tr>
<tr>
<td>Bell et al.32</td>
<td>17</td>
</tr>
<tr>
<td>Meggs et al.33</td>
<td>33</td>
</tr>
<tr>
<td>Voorhees34</td>
<td>17</td>
</tr>
<tr>
<td>Bell et al.35</td>
<td>30 (Gulf War veterans)</td>
</tr>
<tr>
<td>Kreutzer et al.36</td>
<td>15.9 (doctor diagnosed 6.3)</td>
</tr>
<tr>
<td>Caress and Steinemann37</td>
<td>12.6</td>
</tr>
<tr>
<td>Caress and Steinemann38</td>
<td>11.2</td>
</tr>
<tr>
<td>Caress and Steinemann39</td>
<td>11.2 (doctor diagnosed 7.4)</td>
</tr>
</tbody>
</table>

Table 50.4 Prevalence of multiple chemical sensitivity (MCS)

A surprising number of people report sensitivity to ordinary everyday chemicals. The figures range from an average of eleven to seventeen percent, with spikes as high as thirty percent of subjects who report reactions to multiple chemical incitants. The figures reveal that at least two percent, and as many as six percent, have been so bothered by chemical exposures that they sought medical care and received a doctor-diagnosis of multiple chemical sensitivity (MCS). Applying the case definition criteria to the average reported chemical sensitivity, it appears that 1.5 out of 10 people suffer from MCS. Health care utilization costs directly related to MCS have been estimated at approximately $1581 annually per patient. The United States population is estimated to be 302.8 million. Prevalence studies predict that approximately 15% of the United States population, now estimated at 302.8 million, suffers from MCS; therefore, direct health care utilization costs amount to a staggering $71.8 billion dollars per year. Estimated costs for MCS and other disorders linked to neurotoxicity amount to an additional $81.5 to $167 billion annually in lost productivity. Cumulative social and economic costs identified in four case studies of illnesses that are candidates for environmental causation totalled between $568 billion and $793 billion dollars per year.30

& that’s without really treating most of them!
By any criteria, the impact of MCS on individual and community health and the cost to the nation (healthcare budgets) and those directly concerned with the illness (carers and dependants) is considerable.

CHEMICALS INVOLVED

The number and nature of chemicals associated with MCS is huge and covers many different chemical classes, biological activities and sources. Table 50.5 summarizes the major chemicals, their sources and their biological activities. American national studies commenced in 1999, but so far these cover only 148 different compounds. There are important concerns about how to interpret the data and the need to avoid a one-size-fits-all approach. It is necessary to take into account individual factors, including absorption, distribution, metabolism, excretion, genetics, age, sex, environment and nutritional status.

Various studies have found extensive chemical contamination of people throughout the world. Of particular interest is the identification of hundreds of toxic compounds in cord blood, indicating that even in utero, when cellular replication is at its greatest, there is no protection against many very toxic compounds.

Of special note is a report that identified 287 different chemicals in cord blood from newborns. Of these chemicals, 217 were toxic to the brain and nervous system, 208 could cause developmental problems, and 108 cause cancer in humans and animals. American organizations have emphasized the connection between mental retardation and other developmental disorders, including autism-spectrum disorders, and learning and developmental conditions in children, and they stress the lack of any testing of individual chemicals and mixtures for these disorders. Chronic neurological and neuropsychiatric conditions are increasing in older people, possibly as a result of the massive increase in environmental toxins.

The problem was first highlighted in Rachel Carson’s groundbreaking work *Silent Spring*, which was then followed by other publications. Many compounds have been withdrawn but, because of their persistence in the environment and people, contamination is now widespread. For example, PCBs were banned in 1979 in America, but people born after that date are commonly contaminated with these compounds.

A comprehensive study provides considerable data on extensive biological damage to fertility, intelligence and survival as a result of the untrammelled use and irresponsible spread of numerous untested environmental chemicals.

Table 50.5 Major classes of chemicals associated with multiple chemical sensitivity (MCS)

<table>
<thead>
<tr>
<th>Chemical class</th>
<th>Known biological activities</th>
<th>Common sources/uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly substituted, poly- or per-halogenated organic compounds with chlorine, bromine or fluorine atoms*, e.g. DDT, DDE, lindane, hexachlorobenzene, hexachlorocyclohexanes, PCBs, aldrin, dieldrin, PBDEs, perfluorooctanoic acid polymers and derivatives</td>
<td>Carcinogenic, mutagenic, kidney and liver damage, endocrine disruption</td>
<td>Household and agricultural pesticides as sprays and dusts, electrical insulation, flame-retardants, non-stick kitchen utensils, stain-resistant fabrics</td>
</tr>
<tr>
<td>Organophosphates, nerve agents</td>
<td>Nerve toxins, immune dysregulation, inhibition of key enzymes &amp; uses up essential nutrients to metabolise</td>
<td>Various pesticides in agriculture, fisheries, herbicides, engine oils</td>
</tr>
<tr>
<td>Phthalates, nonylphenol, bisphenol A and B*</td>
<td>Endocrine disruption</td>
<td>Polymers, plasticizers, toys, babies’ pacifiers, dialsis tubing</td>
</tr>
<tr>
<td>VOCs, aliphatic and aromatic compounds*, formaldehyde, aldehydes, esters, ketones, acids, alcohols, toluene</td>
<td>Disruption of brain function, nerve damage, carcinogenic</td>
<td>Ubiquitous in fragrances, perfumes, household goods, solvents, fuels, paints, polymers</td>
</tr>
<tr>
<td>PAHs</td>
<td>Carcinogenic, mutagenic</td>
<td>Burning fuels, exhaust fumes, power stations</td>
</tr>
<tr>
<td>Heavy metals: mercury*, lead, cadmium, arsenic, organometallics, tributyltin*</td>
<td>Neurotoxicity, tissue damage, endocrine disruption</td>
<td>Anti-fouling paints, fuels, preservatives, pesticides, electrical goods, crematoria</td>
</tr>
</tbody>
</table>

Many symptoms develop over time as nutrient reserves are depleted & end-organ/system damage occurs. They will also fluctuate depending on depletion of nutrients/exposure to chemicals et al. Nutrient depletion may also lead to inability to handle stress (esp. Zn & B-vits). Stress also leads to further depletion of B-vits - esp. B1 Thiamine & this depletion further lowers capacity to handle chemicals etc.
The challenge is to understand:

- how such diverse chemicals can provoke very sensitive responses to chemically unrelated compounds – this raises new question about drug and chemical receptors and how they operate; & Total Load phenomenon
- how very low levels of exposure well below those affecting the majority of people can provoke such extensive and profound biological effects – this questions the basic understanding of toxicology, particularly the relationship between dose and response and genetics;
- how the damage to one generation can be transmitted to succeeding generations.

In response to these challenges, new mechanisms of drug and chemical action have been proposed, coupled with technologies that provide hidden details of bodily systems, particularly the brain. A further challenge is to understand:

- how so many different chemicals, which have not been evaluated for adverse biological effects, have come to be released for general use; & combined use
- how novel chemicals can be assessed effectively before release into general use.

In response to these challenges, new regulatory systems have been advocated, particularly Registration, Evaluation, Authorisation and Restriction of Chemical Substances (REACH) in Europe. In the USA, action is being demanded to establish a similar regulatory authority. Estimates from various sources indicate that 80,000–100,000 compounds currently used commercially and distributed in a wide variety of products have never been assessed toxicologically or have been assessed only as single entities and not in the complex mixtures in which they are delivered in most products.

Clearly, in addition to the concerns about health, there are important commercial, political and economic considerations around the use and development of chemicals in today’s world. There is no doubt that there is considerable vested interest and even secrecy when MCS is being considered, not only unlike the activities and attitudes around tobacco-smoking, nuclear power, and genetically modified (GM) crops. A big divide lies between those espousing a purely psychogenic, psychiatric or psychological understanding of the illness and those seeking to understand the illness as an organic illness with a clear biological basis.

In marked contrast are the following:

- Stop the 21st Century Killing You
- Chemical Exposures: Low Levels and High Stakes
- Chemical Sensitivity, a large medical publication in four volumes with an allied website.

The website ‘Chemical sensitivity in mainstream medical documentation’ considers all aspects of the debate about MCS, with a strong emphasis on the implications for people who are affected by MCS.

A major two-stage population study of MCS found that only 1.4 per cent of the population studied had emotional problems before exposures occurred, but that after the development of MCS 37.7 per cent of the population had emotional problems, indicating that MCS had a biological rather than psychogenic origin. This is hardly surprising, since any chronic illness is likely to precipitate emotional problems.

THE DEBATE

MCS and other illnesses from a variety of medical specialties have been described as functional somatic syndromes in order to provide a comprehensive scheme for understanding these complex and little-understood conditions/illnesses. This approach has been severely criticized as a disguise for medical ignorance that seeks to label emerging illnesses as psychiatric when they present with symptoms very different from those of established mental illnesses.

It must be noted that there is no proof that it is justified to apply the label somatisation to such conditions as chronic fatigue syndrome and several more illnesses that established medicine has so far failed to explain scientifically... Don’t hesitate to ask questions about scientific evidence behind this talk about somatisation. Be persistent, because a diagnosis of somatisation is definitely not an innocuous label. It will close various doors and lead (to) treatments that usually get nowhere.

Somatisation has a poor track record, being used at one time to ‘explain’ diabetes, Parkinson’s disease, multiple sclerosis and Grave’s disease. All of these now have clear, well-established biological foundations, e.g. Addisons.

The biopsychosocial theory is now offered as the basis for understanding these complex illnesses/conditions. However, although this appears to embrace a more holistic view, one of its major critics states: The biopsychosocial theory lacks an intellectually sound basis, and spells the failure and possible imminent extinction of modern psychiatry.

The intellectual basis for the biological understanding of MCS is found in the neuroendocrine–immune (NEI) paradigm (Figure 50.1). This integrated communication system includes messenger molecules that are released in response to a wide range of challenges. Since these challenges include stress, it is important that the impact of stress is recognized in patients with MCS, but not by denying the...
Numbering signs & symptoms also affected by patients’ and physicians’ lack of adequate terminology - e.g. ME/MCS fatigue VERY different from 'normal' fatigue (& very painful!). Sports medicine more at fault with these states of severe tissue oxidative stress.

- Case criteria were usually formulated only vaguely and were open to multiple interpretations
- … despite all efforts of standardisation … such attempts [were] very limited in clinical-based studies … for each individual case completely different examination may be used which makes standardisation of diagnostic procedures much more difficult.⁵⁰

This final statement points to two different approaches to environmental medicine: (i) a one-size-fits-all approach when considering a patient population and (ii) an approach that sees patients as unique individuals who require individualized medicine for their effective treatment and support.

The study was restricted to volatile organic compound (VOCs) and olfaction and used the 1987 Cullen criteria rather than the more widely agreed 1999 consensus.⁶² Even here, an important study involving capsacin, a classical vanilloid receptor agonist, has been ignored; this study concluded:

Upper and lower airway symptoms induced by chemicals and scents represent an entity of chronic disease, different from asthma or chronic obstructive pulmonary disease, with persistent symptoms, a reduced health-related quality of life and unchanged sensory hyperreactivity.⁶⁰

Other papers conclude that the combined environmental annoyance, smells and electrical equipment is a better predictor of chemical intolerance⁷¹ and that above-average odour discrimination ability was associated with lower ratings of odour intensity and nausea.⁵⁸,⁵⁹

There was no consideration of any possible influence of extensive and multiple contamination by xenobiotics. People from Central Europe were found to carry the highest burden of such compounds.⁷⁶

Additive and synergistic effects of such contamination were not considered. There was no consideration of mutagenic and developmental effects of chemical exposure.⁶⁰-⁶³,⁶⁸,⁶⁹,⁷⁰,⁷¹

There was no consideration of possible brain damage from other widely dispersed toxins such as pesticides.⁷⁴,⁷³,⁷¹

No psychometric tests⁷⁵,⁷¹ appear to have been carried out. Sickness behaviour is well-known to be associated with changes in levels of important cytokines that influence the brain–immune axis,⁶⁰ but this does not appear to have been investigated.

Overall, the firm conclusions are less secure than they may at first appear.

More recent papers report that exposure to VOCs increases plasma levels of vasoactive intestinal peptide (VIP), substance P and nerve growth factors in self-reported MCS patients (mMCS).⁷⁴ Exposure to diesel fumes induced both Th-1 and Th-2 chemokines.⁷⁵

A major conference hosted by the Chemical Injury Information Network (CIIN) provided a comprehensive survey of MCS with copies of important papers in the field.⁷⁶

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**Figure 50.1** The neuroendocrine immune comprehensive integrative defence system

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; IL, interleukin; TNF, tumour necrosis factor; VIP, vasoactive intestinal peptide.

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Biological impact of chemical exposures. Many patients with MCS report high levels of stress if they are disbelieved or falsely accused when seeking medical help for this syndrome.

A German multicentre study on MCS examined 291 consecutive out-patients between 2000 and 2003 in considerable depth and concluded that:⁵⁰

- there was no characteristic set of symptoms for MCS, although many symptoms and clinical signs were identified;
- there was no systematic connection between complaints and any triggers;
- there was no evidence for any genetic predisposition but only metabolic variations in specific alleles;
- there was no obvious disturbance of the olfactory system;
- patients with MCS suffered more often from mental disorders that had commenced ‘many years before environment-related health complaints’;
- ‘overall the study did not support a toxicogenic-somatic basis of the MCS phenomenon’.

These serious and comprehensive conclusions contradict many other studies.⁴⁷,⁴⁸,⁴⁹,⁵⁰,⁵¹,⁵² However, the same study noted some real problems when engaging with MCS:

- A lack of biomarkers, which are now being identified in specific cases⁶⁴,⁶⁵ DNA & ATP neutrophils
- A lack of clear-cut parameters of dysfunction
CONCEPTS AND MECHANISMS

Triggering

Many people with MCS can identify an event when they experienced a large exposure to a toxic chemical, such as a pesticide being sprayed outside or inside the house, a workplace exposure, an accidental spill or an adventitious agricultural spraying. This is followed by an increasing sensitivity to the same or related chemicals and then to quite diverse chemicals in very different situations. Gulf War veterans show an increased incidence of chemical sensitivity and MCS. More than 40 possible battlefield exposures in 1990–91 have been identified, with the major ones being vaccines, pyridostigmine bromide (anti-nerve agent prophylaxis), pesticides (organophosphates, pyrethroids, lindane), nerve agents (sarin, tabun, VX), depleted uranium, oil and smoke. Frequently, veterans develop chemical sensitivity to perfume worn by their partners or children and previously enjoyed by the veteran, to alcohol and to petroleum fumes, which previously was not a problem. The chemistry of perfumes and petroleum products is extensive and diverse and very different from that of pesticides, vaccines and the major Gulf War exposures.

Chronic low-dose exposure to chemicals that may not be apparent to a person can also lead to MCS by a process known as ‘kindling’. Rowat, as part of his proposed integrative defence mechanisms, defines kindling as follows:

Kindling refers to neural processes that mediate lasting changes in brain function in response to repeated, temporally spaced application of neurobehaviorally active agents.

Partial limbic kindling is a progressive and persistent lowering of the threshold for eliciting electrical after-discharges, but not motor seizures, in certain brain structures such as amygdala and hippocampus; behavioral consequences include increased avoidant behaviors.

The range of physical action for kindling includes various brain structures, e.g. the cortex and especially the limbic brain including the olfactory bulb and amygdala. Changes in brain chemistry are found, including a decrease in acetylcholinesterase enzyme activity, that parallels the increase in sensitivity. Calcium-binding protein and tyrosine hydroxylase activity are reportedly reduced, and there are changes in β-noradrenergic binding. Benzodiazepine receptor binding is modified, as are transmitter GABA [γ-aminobutyric acid] and N-methyl-D-aspartate [NMDA] functions. Zinc may be implicated through GABA. Superoxide dismutase may also be involved. These changes may be irreversible.

The blood–brain barrier

The blood–brain barrier is the barrier of endothelial cells lining the blood vessels in the brain (Figure 50.2). The cells possess tight cell junctions that severely restrict access of compounds from the blood into the brain. This is a protective mechanism to restrict entry into the brain of biological and chemical toxins that may be ingested, inhaled or generated by infection in other parts of the body or by injury. There are selective transport mechanisms that supply neuronal and other cells with essential nutrients.

Tight cell junctions occur in other tissues, particularly the gut and the lungs. This protection limits transport across the gut wall (e.g. toxins and infections in food and water) and the lungs (e.g. inhaled toxins), but it is known to be breached by many chemicals, including various pesticides. The blood–testes barrier is similarly breached. The blood–brain barrier is least efficient in the region of the paleolithic brain, and any leakage through the barrier will be greatest in the basal ganglia, brainstem, thalamus, hypothalamus and pituitary gland.

Essential tissue barriers can be opened or bypassed by various mechanisms that are known to be associated with MCS and related overlapping syndromes.

Also NB re nutrients e.g. B12 as metacobalamin passes through blood-brain barrier far more effectively than other forms. NB for MCS, Alzheimers, MMD et al.
Toxicant-induced loss of tolerance

The concept of TILT was proposed as a useful alternative to MCS in 1998 and was fully developed later. A common mechanism is postulated for both drug addiction and multiple chemical intolerance, but with opposite responses: addiction (a demand for regular and repeated doses) and abdication (avoidance of a substance). In both cases, the intent is to avoid withdrawal symptoms associated with a lack or presence of the substance. The basic idea is set out in Figure 50.3, in which the normal response to a stimulant (e.g. caffeine) involves stimulation followed by recovery. Loss of tolerance leads to an increased response, which leads to alternative strategies, abdication (avoidance) or addiction (persistent reinforcing doses).

Miller, in making a case for TILT, relies heavily on the data from various studies involving Gulf War veterans. In particular, she draws attention to the concomitant development of a number of cravings for chocolate, sugar and caffeine in these veterans. This phenomenon has not been commented on previously.

Another aspect of the proposed relationship between abdication and addiction is that dopaminergic, 5-hydroxytryptamine (5-HT) and opioid neural pathways in the brain are associated with addiction and the response to addictive drugs and food. These same pathways are damaged in Gulf War veterans, & OP agricultural victims.

Volatile or aerosolized inhaled substances may be carried by intraneuronal transport along the olfactory tract directly into the limbic system (Figure 50.4). This bypasses the blood–brain barrier and introduces compounds directly into deep (silent) brain structures where many basic bodily responses are controlled.

Allergy, neurogenic inflammation and switching

The association of MCS with allergy has been the subject of considerable debate, concerned mainly with the definition of allergy. One common scheme recognizes four kinds of allergy and hypersensitivity:

- **Type 1:** mediated by immunoglobulin E (IgE) and almost immediate (2–30 min). May lead to systemic anaphylaxis, which can be life-threatening, or to more localized anaphylaxis (e.g. insect bites, hay fever, asthma, hives, eczema, food allergies). IgE interacts with specific cells (basophils, mast cells), which are stimulated to release potent vasoactive mediators such as histamine and leukotrienes.

- **Type 2:** antibody-mediated. The antibodies immunoglobulin G (IgG) and immunoglobulin M (IgM) attack sites on cell walls, leading to total destruction of the cell. This process takes 2–8 h. The cell damage or loss can be very serious. Examples include blood-transfusion reactions and some types of anaemia.

- **Type 3:** involves antigen–antibody (IgG) complex formation and takes 2–8 h. The antigen–antibody complex precipitates in various tissues and induces an inflammatory reaction. Examples include a number of chronic illnesses, including glomerulonephritis, rheumatoid arthritis and systemic lupus erythematosus (SLE). A delayed response to insect bites or vaccines may operate by this mechanism.

- **Type 4:** cell-mediated. Hypersensitivity is slow (24–72 h). It involves sensitized immune cells, special T-cells that release chemical messengers (cytokines) that activate other immune cells, causing direct cell damage. Contact dermatitis, tubercular lesions and graft rejection are examples.

Not uncommonly, a single chemical or group of chemicals can induce more than one type of allergic response, for example penicillins can cause types 1–4 reactions.
Meggs and colleagues define allergy as a type 1 reaction. They regard MCS as the opposite side of the coin, sharing a similar mechanism to allergy.97,98

- The response to an allergen or a chemical irritant is not limited to the immediate site of application or entry. For example, about 2 per cent of people with asthma have their asthma triggered by eating certain foods or alcohol.99 The inoculation of the gut leads to a response in the lungs: Meggs calls this ‘switching’. Bee stings may cause a generalized reaction involving the whole body and not only the local area affected by the sting itself. Similarly, chemicals that are generally inhaled can cause diverse symptomatology associated with the central nervous system, headaches, pain, rashes and gastrointestinal disturbances.

Adaptation is a key four-stage construct in chemical exposures that has been known from the 1950s. The removal of the offending chemical(s) will lead to recovery, except at stage 3:

- **Stage 0**: exposures are tolerated without illness.
- **Stage 1**: exposure leads to multiple complaints, e.g. headache, nausea, itching, flushing.
- **Stage 2**: inflammation occurs in one or more organs, e.g. rhinitis, asthma, arthritis, myositis (inflammatory muscle disease). Continued low-dose exposure at this stage will propagate the inflammatory condition(s).
- **Stage 3**: fibrosis with tissue damage, irreversible lung disease, advanced asthma, deforming arthritis, etc. All the major systems can be affected, including musculoskeletal, respiratory, cardiovascular, gastrointestinal, genitourinary and nervous.

Conditioning is a feature of MCS. In chemical sensitivity, the most common classes of chemicals to trigger a reaction are volatile and odorous. The odour threshold is many times lower than the chemical irritancy threshold, and this may explain the large difference in exposure levels that develop in people with MCS.

Essentially, chemical irritants bind to receptors on unmyelinated sensory nerve C-fibres, which are found in the gut, airways, eye and genitourinary system and are more numerous in patients with MCS. Binding triggers an inflammatory response via an axon reflex, leading to release of substance P and subsequently other localized mediators of inflammation by interaction with mast cells (Figures 50.5 and 50.6).

Central pathways also activate parasympathetic or sympathetic nerves with effects on more distant organs.98 Meggs and colleagues make much use of data from studies on Gulf War veterans; they report extensive intolerance to petrol, diesel, oils and exhaust fumes.99 Many veterans describe their response as loss of awareness (‘spaced out’), loss of motor control and ataxia. In some cases, this was so marked that driving became dangerous. Some veterans are unable to fill up their vehicle at a petrol station because this would render them incapable of driving safely. Mortality or masking

**apparent (often relapse if not repaired)**

**and their intracellular nutrient status**

studies on Gulf War veterans show that there is an excess of deaths from motor vehicle accidents in this group.27 Although this has been dismissed by the UK Ministry of Defence (MoD) and the US Department of Defense (DoD) as a legacy of military service resulting in extravagant and risk-taking behaviour and an inability to cope with a return to civilian life, no other explanation has been forthcoming. MCS offers another explanation that better accords with the evidence and military training, which requires that extravagant risks be avoided and makes motor control and awareness paramount.

A useful summary of the varied responses to chemical exposures is given in Figure 50.7. This includes the recognition of the importance of perception and central integration of the experience (Figure 50.8).

Glutathione/Selenium +++ required to control/repair

it also occurred in Agricultural and office/workplace/home solvent initiated poisoning et al
Damage to deep brain structures

Haley found clear evidence from MRS of cell death in the basal ganglia and brainstem of sick American veterans from the first Gulf War (Figure 50.9). Later studies in animals and from historical exposures found more areas of the brain to be damaged, leading to the conclusion that ‘While preliminary, such findings raise the concern that ill Gulf War veterans may have neuronal damage in multiple regions of the brain.’ Undoubtedly, the major chemicals involved are inhibitors of acetylcholinesterase, organophosphate insecticides, the nerve agent sarin and pyridostigmine bromide – the so-called ‘cholinergic triple whammy.’ A useful paper analyses studies of sick veterans, agricultural workers and shepherds.

Damage to the deep brain structures is consistent with penetration of the blood–brain barrier by toxic chemicals either via the bloodstream or by intraneuronal transport but leads to biotransformation and downward spiral of overall health if not treated.

What about intracellular nutrient status as part of this paradigm?

**DAMAGE TO DEEP BRAIN STRUCTURES**

Figure 50.7 Summary of responses to chemical exposures. (a) More sensitive = a decrease in the magnitude of exposure required to initiate the response; more reactive = an increase in the slope or in the maximum level of the exposure–response curve. (b) The threshold for perceiving symptoms may occur in the mid-position of the exposure–response curve (T). As a result, the clinical report of increased sensitivity could mean that the individual has become more reactive (R) or more sensitive (S). (c) Recognition of symptoms may require the response to be present for a certain duration. The clinical report of increased sensitivity could mean that the response has become more prolonged. (d) Habituation = decreasing responses with single repeat exposures; adaptation = progressive decrease in magnitude of response with prolonged exposure.

Figure 50.8 Potential interactions between chemical sensitivity and the domains of neurogenic inflammation, perceptual and central integration, and non-neurogenic inflammation.

Figure 50.9 Basal ganglia wrapped round the thalamus, deep in the brain.
along the olfactory tract, as suggested by Ashford and Miller. Undoubtedly, veterans of the first Gulf War were exposed to a large number of diverse chemical and biological toxins and considerable electromagnetic radiation from many sources. Some 25–30 per cent of these veterans are now ill, and for this to happen to healthy young people in the prime of life serves as a warning to the whole of society about taking care with the manner in which we expose even the healthiest people to novel chemicals. The counter view, that seeks to establish Gulf War illness (GWII/GWS as a psychiatric illness, is typical of the debate that rages around MCS in the face of incontrovertible and replicated evidence of significant brain damage in sick Gulf War veterans. It is important to examine the implications for mental health rather than to claim that there is no such evidence.

LIR Tomography on MCS/ME patients shows serious Δs

METABOLISM AND CHEMICALS

The liver is the main but not the only organ of metabolism and is crucial in removing both endogenous and exogenous compounds/xenobiotics from the body. Metabolic processes are generally well understood and involve a range of established chemical reactions. Of particular importance is a two-stage process involving phase 1 and phase 2 metabolism. Phase 1 involves a large family of haem-containing enzymes, mono-oxygenases and cytochrome P450 enzymes (CYP450), which introduce oxygen atoms into organic compounds that are largely lipid-soluble, creating highly reactive intermediates. In phase 2, these intermediates undergo conjugation with a variety of molecules to generate water-soluble products that can be excreted in the urine (Figure 50.10). An important but secondary process involves excretion of some lipid compounds in the faeces.

Human CYPs play an important part in the transformation of many key endogenous compounds (e.g. steroidogenesis) but they have been studied most widely in connection with drug metabolism and some carcinogenic compounds (e.g. polycyclic aromatic hydrocarbons, PAHs). The metabolism and elimination of xenobiotics is now an important area of toxicology. CYP450s are involved in the metabolism of about 75 per cent of drugs and xenobiotics and are present in many important areas in the body, including the mitochondrial membranes, the blood–brain barrier, the gastrointestinal tract and the liver. Many xenobiotics distributed widely in the environment are PAHs. Phase 1 metabolism transforms PAHs via the introduction of active oxygen species into very reactive compounds such as epoxides, which in turn undergo phase 2 conjugation into more polar compounds, which can be excreted in the urine. If oxidative phase 1 processes are not controlled carefully and coupled with phase 2 reactions, then destructive reactive oxygen species (ROS) are produced, leading to oxidative stress, which can cause considerable tissue damage - a feature of all complex multi-system illnesses. Reliable data

Muscle and connective tissue are major sites, not just liver - hence muscle pain & SC lumps/tumours/cysts & vasculitis & sweat, tears, or deposited in hair (especially heavy metals)
are available for ME/CFS, organochlorine pesticides and organophosphate pesticides, alone or in combination with xenobiotics. Both mitochondrial function and the nervous system are affected.

Oxidative stress, defined as an imbalance between reactive oxygen species and free radicals and antioxidant compounds, can also arise from other defence processes such as inflammation, which are also tightly controlled under normal circumstances.

This insight into multi-system illnesses suggests useful ways of providing treatment for patients with MCS.

Bioactivation can be a result of the metabolic conversion of xenobiotics ( aflatoxins) and drugs (ethyl carbamate, troglitazone, terfenadine) to more toxic compounds. In contrast, many persistent and bioaccumulative compounds possess bonds that are resistant to cleavage in metabolic reactions. This is particularly true of carbon–halogen bonds attached to aromatic or ethylenic carbon atoms. Such compounds accumulate up the food chain, leading to increasing doses in the organisms, including humans, that are at the top of the food chain. Significant contamination of fish oils with PCBs and dioxins and of tuna and swordfish with mercury have been reported, leading to advice to restrict the intake of these foodstuffs. Mercury is both concentrated and bioactivated to methyl mercury when it passes up the food chain, and this was the cause of the severe neurotoxic/psychiatric Minamata disease.

Phase 2 metabolism assists the elimination of many compounds by conjugation of reactive chemical groups present in endogenous and exogenous compounds. The classical example is paracetamol. The metabolic pathway involves conjugation with sulphate or glucuronol groups, but when these become exhausted in patient who has taken an overdose, a toxic quinoneimine is formed, which binds to glutathione, the primary cellular antioxidant molecule. The progressive removal of glutathione is responsible for the slow but often inevitable fatal effects of paracetamol.

### GENETICS

ME/CFS has been investigated extensively by Kerr and colleagues, who have identified some 88 genes that are mainly up-regulated in very sick patients with ME/CFS. The larger study identified seven clinical phenotypes for ME/CFS. Although such studies have yet to be carried out on patients with MCS, there is evidence of genetic susceptibility in some studies. e.g. Dr Sholets etc.

The importance of genetic variations in drug- and xenobiotic-metabolizing enzymes was recognized at the beginning of the twenty-first century.

The underlying genetic predisposition of each patient will reflect combinations of poor- and extensive-metabolizer phenotypes; if these enzymes cooperate in the same metabolic pathway for any given drug or environmental agent, such ecogenetic variability might be synergistic and lead to as much as 30- or >40-fold differences in activation or degradation. The end result can be large interindividual differences in risk of environmentally caused toxicity or cancer.

In one study, there was an 18-fold increase in the risk of MCS when interactions between CYP2D6 and NAT2 metabolizing enzymes occurred. Another study found that variations in NAT2 and GST genes were linked to increased chemical sensitivity. One study did not find any link with some allelic frequencies, but it considered only NAT1, NAT2, PON1 and PON2 and did not consider CYP2D6 or GST genes. Because of the large number of genetic variants of the many enzymes involved in xenobiotic metabolism, this is a complex but urgent area of study that will be very fruitful in understanding the widespread variations in MCS. Analogous studies to those of Kerr and colleagues are urgently needed.

Although traditionally the major concern has been with drug metabolism (pharmacogenomics), the wider term ‘toxicogenomics’ has been introduced, and a paper describes how exposures to arsenic in drinking water can alter the function in babies born to mothers exposed in this way. This disturbing link of arsenic exposure to increased inflammatory responses in the succeeding generation increases the urgency to recognize and treat MCS, of which it is a part.

The enzyme paraoxonase 1 (PON1) has been particularly well studied. It plays a key role in protecting against oxidative stress associated with the oxidation of low-density lipoprotein. It is now recognized as a key enzyme in removing organophosphates and nerve agents from the body. It is important in GWS, where initially it was proposed that genetic variants Q and R, respectively involving the amino acids glutamine or arginine at position 192 in the enzyme, were important. Soon, however, it was found that it was the level of the enzymes and not their genetic form that was important. The use of leaded petrol in the Gulf War may well have depressed the levels of PON1, making the troops more susceptible to the toxic effects of organophosphates and nerve agents. This illustrates the complexity of MCS where two apparently independent factors have been found to impact on the same biological system. Later studies indicated that there is genetic control of the levels of the enzyme produced, particularly in connection with the recognition of organophosphates in aerotoxic syndrome.

### Polymorphisms

Polyorphisms are defined as variations in gene structure that are too common to be due merely to new mutations. A polymorphism must have a frequency of at least 1 per cent in the population. They have become the subject of intense research, as small changes in gene structure can now be identified that have been associated with the risk of developing chronic diseases in later life and also predicting the
consequences of gene–environment interactions. In single-nucleotide polymorphisms (SNPs), a single nucleotide change occurs that alters the function of the gene; for example, in the PON1 gene, the trinucleotide sequences for the key amino acids at position 192 in the enzyme are glutamine (CAG) and arginine (CGG) and involve the single exchange of adenine (A) for guanosine (G). However, it is now clear that almost 200 polymorphisms have been found in PON1, although not all are functional. The direct measurement of the enzyme itself is the most reliable way of investigating its role in disease:

We, along with other authors, would strongly suggest that all further epidemiological studies into the role of PON1 and disease should include a measurement of the enzyme itself in addition to the genetic polymorphisms.

This conclusion is a measure of the difficulties of investigating complex multi-system illnesses such as MCS.

**Epigenetics**

Epigenetics concerns changes in the phenotypic expression of inherited genes by chemical modification of DNA and chromatin, which results in changes of gene function (transcription, replication, translation, combination). Such modifications involve methylation of DNA or methylation, acetylation, phosphorylation, ribosylation or ubiquitination of chromatin. These processes result in remodelling of chromatin, with subsequent changes in gene expression. Genes may be silenced or activated by these processes, which can cause permanent and heritable, or transient, changes in the phenotype. These changes can occur throughout life: preconceptually, in either parent; periconceptually; early or late gestation; and in neonates, children, young adults and older adults. Animal and epidemiological studies have identified changes in the reproductive organs, uterus and mammary glands, including cancers in later life (diethylstilboestrol, DES; bisphenol A, BPA), prostate problems (methoxychlor), sperm-counts, fertility problems, hypospadias (phthalates), nutritional effects, obesity (DES, tributyltin (TBT), BPA) and early-onset parkinsonism (paraquat, maneb). The major factors are presented in Figure 50.11.

It is a matter for concern that the nutritional status of the mother may have serious developmental outcomes for her offspring when they reach adult later life (Figure 50.12). Combined with these adverse developmental effects, environmentally encountered heavy metals such as arsenic, manganese and lead will exacerbate the deficits imposed on children, particularly in the developing world, where parents, especially mothers, are under prolonged
socioeconomic stress. This avoidable loss of human potential is a grievous loss to the world community.

**Mitochondrial DNA**

Mitochondrial DNA is derived only from the mother and is known to more readily undergo mutations and damage compared with nuclear DNA. Pathogenic mutations in mitochondrial DNA have been reported to be common. The question arises as to what effects environmental toxins have in this process. Are epigenetic changes involved? Since oxidative stress, a feature of MCS, is associated with compromised mitochondrial function, these latest findings may be very important for the future, and readily tested.

**THE NO/ONOO HYPOTHESIS**

Pall brought together a long series of papers and reviews concerning the NO/ONOO (nitric oxide/peroxynitrite) hypothesis [Figure 50.13]. This provides a comprehensive disease paradigm for ME/CFS, MCS, fibromyalgia, post-traumatic stress disorder (PTSD), GWS and related illnesses.

![Figure 50.13 NO/ONOO (nitric oxide/peroxynitrite) cycle](image)

Table 50.6 shows some conceptual shifts in toxicology.

**Low-level exposure**

There are many examples of low levels of exposure having significant effects on biological organisms and humans some 100-fold lower than the no observable adverse effects level (NOEL or NOEL) or allowed daily intake (ADI). TBT(O) Tributyltin, with a NOEL of parts per billion (ppb), caused sterility in dog whelps at 20 parts per trillion (ppt), while permethrin, with an ADI of 0.7 parts per million (ppm) killed most water invertebrates at 5–10 ppb. In mammalian systems, endocrine-disrupting chemicals with oestrogenic activity evoke responses at very low doses, comparable with those found in the environment and consumed by people, but higher doses had contradictory effects, making it essential to develop biological testing systems that will be responsive to low doses of environmental toxins. An important aspect of testing chemically sensitive people is the need to allow a period for adaptation before exposures in order to ensure reliable and reproducible experimental measurements.
Additivity, antagonism, synergism, non-monotonic dose–response curves and hormesis

Environmental toxicants are usually encountered in complex mixtures, but most are tested individually. The combined effects of such compounds might be expected to be additive, antagonistic or synergistic. The study of these relationships is complex and varied, but examples of such interactions have been found experimentally in whole animals and in isolated biological in vitro systems:

- **Additivity**: using a yeast oestrogen screen, the effects of four different oestrogenic compounds (4-nonylphenol, 4-octylphenol, \( o,p \)-dichlorodiphenyltrichloroethane (DDT), genistein) in two to four component mixtures were found to be additive.\(^{149}\)

- **Antagonism**: this was described in a study of the teratogenic effects of mixtures of PCBs.\(^{150}\) It was found that the immunotoxic effects of one PCB congener were antagonized by another closely related congener.

- **Synergism**: this arises when the overall toxic effects of a mixture are greater than the sum of those of the individual components. This has been observed with acetylcholinesterase inhibitors and \( N,N \)-diethyl m-toluamide (DEET), an insect repellent used in the first Gulf War in 1990–91,\(^{151}\) in pesticide formulations\(^{152}\) and in herbicide formulations.\(^{153}\) The so-called ‘inerts’ in product formulations can increase toxicity and should be included in routine testing of any products, which commonly involves only a single active ingredient. These effects can be very large, with increases in toxicity of more than 100- or 1000-fold. Disturbingly, commonly used food additives also show synergistic increases in developmental neurotoxicity tests.\(^{154}\)

- **Non-monotonic dose–response curves**: classical toxicology uses linear dose–responses to estimate the limits for exposure to environmental toxins (Figure 50.14). This effect involves the assumption that dose–response is linear and, at a sufficiently low dose, becomes zero – the NOEL. The data, usually from animal experiments, are then adjusted arbitrarily by reducing the identified dose by one or more orders of magnitude in order to obtain the reference dose. The reference dose is chosen to accommodate possible differences between animal and human responses, and the different sensitivities of children and elderly people. The NOEL is, in this way, reduced to an estimated reference dose some 100–1000 times lower than the observed experimentally determined dose.

<table>
<thead>
<tr>
<th>Old concept</th>
<th>New concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-level contamination overwhelms detoxification and other defence mechanisms</td>
<td>Low-level contamination hijacks control of development</td>
</tr>
<tr>
<td>The dose makes the poison</td>
<td>Non-monotonic dose–response curves are common, in which low-level exposure causes effects that disappear at higher levels</td>
</tr>
<tr>
<td>Only high levels of exposure matter</td>
<td>Impacts caused at what had been assumed to be background levels</td>
</tr>
<tr>
<td>Focus on adults</td>
<td>Periods of rapid growth and development (prenatal through puberty) are most sensitive to exposure</td>
</tr>
<tr>
<td>A small number of ‘bad actors’</td>
<td>Many chemicals previously thought safe are biologically active and capable of interfering with signalling systems</td>
</tr>
<tr>
<td>Immediate cause and effect</td>
<td>Long latencies are common; fetal programming can lead to disease and disabilities decades later</td>
</tr>
<tr>
<td>Examine chemicals one compound at a time</td>
<td>In real life, mixtures are the rule; they can lead to effects at much lower levels than indicated by simple experiments with single chemicals</td>
</tr>
<tr>
<td>Focus on traditional toxicological endpoints such as mutagenesis, carcinogenesis and cell death</td>
<td>Wide range of health endpoints, e.g. immune system dysfunction (hyper-/hypo-active), neurological/cognitive/behavioural effects, reproductive dysfunction, chronic diseases</td>
</tr>
<tr>
<td>One-to-one mapping of contaminant to disease or disability</td>
<td>Same contaminant can cause many different effects, depending upon when exposure occurs during development and what signals it disrupts; multiple contaminants can cause the same endpoint if they disrupt the same developmental process also depends on nutrient status!</td>
</tr>
</tbody>
</table>

& due to progressive depletion of nutrients & damage to detox pathways & blocking of same may also be a factor in ES as myelin sheaths & lipoprotein layers in membranes affected/compromised
underlying mechanisms of action, and not simply empir-
stimulatory effects are not always beneficial and may be
any health decisions based on beneficial effects must
all the induced effects of a toxicants, and not only the

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Saal and colleagues wrote (author’s italics):

Figure 50.15 Different linear and non-monotonic dose–response curves

The situation is complicated by the discovery of two
classes of oestradiol receptors, one in the nucleus and one
that is membrane-bound. The membrane-bound receptor is
equally sensitive to oestradiol and bisphenol A, while the
nuclear receptor is much less sensitive to bisphenol A.158

The crucial nature of the test systems must be considered
when determining the NOEL and reference doses.

Hormesis

Hormesis is defined as low-dose stimulation and high-dose
inhibition and follows a non-monotonic dose–response curve. It has been used to claim that low doses of environ-
mental toxins should be regarded as beneficial and be the
default position adopted by regulators and clinically. There
has been a thorough evaluation of this view, which emphaz-
sizes that:159

- underlying mechanisms of action, and not simply empir-
ical data, must be considered;

- stimulatory effects are not always beneficial and may be

harmful;

- any health decisions based on beneficial effects must
address interindividual differences, including suscepti-
bility, genetic factors, life stage and health status;

- any health decisions based on beneficial effects must
address the fact that other environmental and workplace
exposures may alter the low-dose response of a single
agent.

This excellent paper puts all these considerations into a
generalized theoretical framework and includes many
telling experimental examples. For instance, 2,3,7,8-tetra-
chlorodibenzodioxin (TCDD), an environmental carcinogen,
had been quoted as having low-dose beneficial effects. Closer examination of the data shows this to be false, since
the incidence of tumours of the liver, lung, tongue and
nasal turbinates increased, while incidence of tumours of
the pituitary, uterus, mammary glands, pancreas and adre-
nal glands decreased.

In one study claiming the hormetic effects of cadmium, a
non-statistical decrease in testicular cancer in rats was
accompanied by a statistical increase in prostatic hyperpla-
sia and an increase in prostate tumours per animal in the
hormetic range.

Ethanol is cited as a classic hormetic agent, since benefi-
cial outcomes – reduced risk of coronary heart disease and
a reduction in mortality – have been identified with low
consumption, in contrast to increases at higher doses of,
among other things, neurological disorders, cancers and
liver cirrhosis. However, small amounts of alcohol (0.5 units
per day) in pregnancy have been associated with adverse
behavioural outcomes such as aggression in children,

Part 4: Mental health problems and mental illness

The challenge to toxicology
Developmental effects of environmental exposures

Intergenerational effects
Diethylstilboestrol (DES) is known to cause malformation of the uterus in daughters born to women who received DES during pregnancy, predisposing the daughters to rare uterine cancers. In rats, androgen receptors were permanently raised in male offspring of females given DES during pregnancy, with an increase in the size of the prostate gland. BPA caused similar changes. DDT lengthened the time to pregnancy (fecundability) in the daughters of mothers exposed to DDT; the probability of pregnancy fell by 32 per cent per 10 μg/L in maternal serum.164

Effects on the fetus and babies
The most rapid multiplication of cells and differentiation of tissues occurs during fetal growth and development within the womb. This is when key biological processes are most susceptible to disturbance by xenobiotics. The notion that the developing fetus is protected during its growth and development within the womb has been shown to be wrong. Many xenobiotics cross the placental barrier and can disrupt many crucial stages of development.

A ruling by the USA high court awarded damages of $4 million to John Castillo, who was born without eyes (anophthalmia) following his mother's exposure to the fungicide benlate when she was 6–7 weeks' pregnant with her son. The exposure occurred on a single day when Mrs Castillo was accidentally sprayed while walking. The initial case was hotly contested by DuPont, the manufacturer of benlate, but the case was upheld and then lost on appeal before the final ruling of the Florida supreme court in 2003. The time of the exposure in the Castillo case corresponded to the time of maximum cellular replication and organogenesis in the developing fetus. The company had funded a 2002 study that showed benlate to be concentrated in the eyes in rats. This report was unpublished but reported by the Guardian newspaper. Benlate has been the subject of numerous other cases and has now been withdrawn, after 33 years on the market.

Cord blood studies identified hundreds of toxins to which the fetus had been exposed, many of them developmental neurotoxins. This is of particular concern to the American Association on Mental Retardation (AAMR; now the American Association on Intellectual and Developmental Disabilities, AAIDD), which stated: ‘The evidence is mounting that exposure to environmental pollutants and toxins are contributing to poorer health and significant increases in chronic disease and disabilities in our society’. Some 17–18 per cent of Americans under age 18 years are claimed to be affected.164

A scientific consensus statement on environmental agents associated with neurodevelopmental disorders brings together the most up-to-date information of a large group of concerned scientists in the USA and emphasizes the following:165

- Children and young people cannot be considered as ‘small adults’ and show marked differences in physiology and routes of exposure. They are often more susceptible to environmental exposures.
- Low doses of toxicants can alter gene expression and affect learning and development.
- Effects can be delayed.
- Genetic polymorphisms render some subgroups more sensitive than others to certain chemicals.

Autism, attention deficit hyperactivity disorder (ADHD) dyslexia, mental retardation, lowered intelligence quotient (IQ) and other disorders of learning and behaviour are highly prevalent among American children. These conditions appear to be rising, with presently 5–15 per cent of all children under the age of 18 years in the USA affected – more than 12 million children. ADHD has been shown to be linked to food additives used in children’s drinks and foods.166 Autism-spectrum disorder appears to be ten times more prevalent now than in the 1980s. The costs of providing special educational services in the USA have been estimated at $77.3 billion, twice the cost of regular education. In addition, there is the human cost for families and communities.

Agents definitely found to be associated with learning and development disabilities (LDDs) are alcohol, lead, mercury, manganese, arsenic, PCBs, polybromodiphenylethers (PBDEs), solvents, PAHs, pesticides and nicotine in tobacco smoke. The damaging effects of these toxins have been known for many years, but the development of products containing them has been allowed to take place on economic grounds. A good example is lead. The toxic neurodevelopmental properties of lead have been known for years; however, its use in paints and in petrol was stopped only after much struggle. The failure of policy-makers to protect young children by not acting quickly in response to the science has laid waste countless young lives. The Centers for Disease Control and Prevention (CDC) has not changed the standard for acceptable blood levels of lead in children since 1985, although the most recent proposal for a level of 2 μg/dL is some 12.5 times lower than the 1985 level.

Solvents and solvent-based products (Table 50.7) are frequently involved as neurotoxins and are ubiquitous in the environment.

Effects on elderly people
The Pritchard Report examined changing patterns of adult (age 45–74 years) neurological deaths in the major Western world in the period 1979–97 and found significant increase in chronic illnesses, for which the report suggested possible environmental factors.37
Delayed effects

One of the most worrying aspects of chemical exposures and MCS is the development of delayed neurotoxic effects years after the initial exposure, which may have been at low levels. This has been found with GWS\textsuperscript{66} and in survivors of terrorist attacks using the nerve agent sarin.\textsuperscript{129,166–168} Such temporal relationships are easily missed without a very thorough history.

Table 50.8 Top 12 treatments tried in multiple chemical sensitivity (MCS)

<table>
<thead>
<tr>
<th>Treatment tried</th>
<th>n</th>
<th>Harmed (%)</th>
<th>No effect (%)</th>
<th>Helped (%)</th>
<th>Helped/harm ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical-free living space</td>
<td>820</td>
<td>0.6</td>
<td>4.5</td>
<td>94.8</td>
<td>155.2</td>
</tr>
<tr>
<td>Chemical avoidance</td>
<td>875</td>
<td>0.8</td>
<td>4.7</td>
<td>94.5</td>
<td>118.6</td>
</tr>
<tr>
<td>Prayer</td>
<td>609</td>
<td>1.4</td>
<td>34.4</td>
<td>64.2</td>
<td>48.3</td>
</tr>
<tr>
<td>Meditation</td>
<td>423</td>
<td>2.8</td>
<td>43.3</td>
<td>53.8</td>
<td>19.2</td>
</tr>
<tr>
<td>Acupressure</td>
<td>308</td>
<td>4.5</td>
<td>28.3</td>
<td>67.2</td>
<td>14.9</td>
</tr>
<tr>
<td>Touch for health</td>
<td>75</td>
<td>3.8</td>
<td>41.8</td>
<td>54.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Air filter (to prevent exposure)</td>
<td>786</td>
<td>6.0</td>
<td>11.8</td>
<td>82.1</td>
<td>13.7</td>
</tr>
<tr>
<td>Rotation diet</td>
<td>560</td>
<td>5.7</td>
<td>22.1</td>
<td>72.2</td>
<td>12.7</td>
</tr>
<tr>
<td>Acidophilus</td>
<td>661</td>
<td>4.1</td>
<td>44.0</td>
<td>52.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Relocation</td>
<td>513</td>
<td>7.4</td>
<td>6.0</td>
<td>86.6</td>
<td>11.7</td>
</tr>
<tr>
<td>Reflexology</td>
<td>204</td>
<td>4.8</td>
<td>38.5</td>
<td>56.6</td>
<td>11.6</td>
</tr>
<tr>
<td>Personal oxygen to cope with exposures</td>
<td>326</td>
<td>7.3</td>
<td>14.2</td>
<td>78.4</td>
<td>10.6</td>
</tr>
</tbody>
</table>

A survey of 917 people with MCS enquired about illness rating: the results were mild (7%), moderate (32%), severe (49%) or totally disabling (13%), with the respondents being mainly white (95%) and predominantly women (82%).\textsuperscript{169} A total of 101 treatment and management techniques procedures, and their perceived efficacy, were assessed. A help/harm ratio was devised that allowed comparison of the different treatments tried by the respondents (Table 50.8). The higher the ratio, the more helpful the treatment, with a ratio of 10 indicating that ten times more people found the treatment helpful compared with those who found it harmful. The lower the ratio, the more harmful the treatment, with a ratio of 0.1 indicating that ten times more people found the treatment harmful compared with those who found it helpful. A ratio of 1 indicates that there was an equal balance between help and harm.

The three most highly rated treatments were:

- a chemical-free living space (ratio 155.2);
- avoidance of chemicals (ratio 118.6);
- prayer (ratio 48.3).

Other reports emphasize the importance of a chemical-free living space and avoidance of chemicals in health, education, legal and benefit provisions.\textsuperscript{21,22,27,28,40,61,62} It is clearly common sense to avoid known chemicals that cause the patient problems and to avoid contact with other chemicals on the precautionary principle. Chemical-free living space is humane and less costly than attempting to provide long-term medical care for this complex condition. The inclusion of prayer is striking and indicates the need to consider & nutrition! IV if necessary! & oxygen use

<table>
<thead>
<tr>
<th>Mostly solvent-based</th>
<th>Partially solvent-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasoline</td>
<td>Glues</td>
</tr>
<tr>
<td>Diesel fuel</td>
<td>Adhesives</td>
</tr>
<tr>
<td>Charcoal lighter fluid</td>
<td>Oil-based paints</td>
</tr>
<tr>
<td>Lantern fuel</td>
<td>Fingernail polish</td>
</tr>
<tr>
<td>Grease</td>
<td>Furniture polishes</td>
</tr>
<tr>
<td>Lubricating oils</td>
<td>Floor polishes and waxes</td>
</tr>
<tr>
<td>Degreasing agents</td>
<td>Spot removers</td>
</tr>
<tr>
<td>Paint strippers</td>
<td>Metal and wood cleaners</td>
</tr>
<tr>
<td>Paint thinner</td>
<td>Correction fluid</td>
</tr>
<tr>
<td>Turpentine</td>
<td>Computer disk cleaners</td>
</tr>
<tr>
<td>Nail-polish remover</td>
<td>Varnishes and shells</td>
</tr>
<tr>
<td>Rubbing alcohol</td>
<td>Wood and concrete stains</td>
</tr>
</tbody>
</table>

\textsuperscript{50-Psychiatry_Evidence_Based-ccp:9780340950050 6/10/09 18:27 Page 811}
people with MCS holistically. Prayer is not defined in any specific terms but excludes meditation, hypnosis and faith healing. Cognitive-behavioural therapy (CBT) is not considered specifically, but psychotherapy as a cure is rated as of no noticeable effect (65.3%) or as very harmful (6.6%). However, as a coping procedure, 47.7% per cent of patients found psychotherapy somewhat helpful, with 24.1% per cent of patients reporting no noticeable effect. Exercise is reported as causing harm (14.7%), of no noticeable effect (23.7%) or helpful (61.6%). Exercise is reported by severely ill people with ME/CFS to be positively harmful, with only 5 per cent of patients finding it helpful.170,171

The interventions rated as more harmful than helpful include:

- conventional medicines, particularly all antidepressants and anxiolytics (tricyclics, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines) and anti-seizure drugs (help/harm ratio 0.1–0.5);
- provocation-neutralization (P-N) testing for chemicals with preservatives (help/harm ratio 0.9).

Since MCS includes heightened sensitivity to chemicals, it is not surprising that the response to drugs is also heightened. When any drugs are given, it is imperative that the initial dose is much lower (one-quarter to one-eighth) than the starting dose recommended in the formularies in order to avoid any possible (severe) reactions. The drugs generally found harmful are those that work by modifying brain function, which is a major area of damage in MCS and part of the neuroendocrine immune paradigm.

More surprising was the inclusion of P-N among the more harmful treatments. P-N is used widely and commended among some practitioners of ecological/environmental medicine.61,62 P-N can take different forms, but these were not specified.

Initially, saunas were three to four times more helpful than harmful and feature among the recommended treatments that offer a means of detoxification.61,62,66 However, over a longer time, saunas proved less helpful. The type of sauna used (wet or dry) was not specified. Reducing the total toxic load is seen as a desirable goal in treatment.61,62,86,96,172,173

Diet was also generally helpful. Only a rotation diet was mentioned, although other exclusion diets, in which dairy and gluten are the first to be removed, using a food diary61,62,86 or following the Stone Age diet62 may also be helpful. Other aspects of diet modification include using acidophilus to support gut flora, which, with related probiotics, features in many diets.

Detoxification includes removal of dental fillings, with a help/harm ratio of 4.8, and the use of UltraClear®, a combination product designed to comprehensively support the gut, with a health/harm ratio of only 1.

Many people had tried a range of mineral, vitamin and co-factor combinations were used. One study found that MCS was not associated with vitamin deficiency or thyroid function, but lower lymphocyte counts suggested immune dysfunction with VOCs.160 The advent of specific tests that allow the identification of toxins permits more precision in designing treatments. Such tests identify blockade of mitochondrial function, DNA adducts161–175 and analysis of needle-fat biopsies. Pesticide load has been reduced by choline and vitamin C.177 Vitamin B2 has long been used to treat neuropsychiatric disorders where no anaemia or macrocytosis is present.

Various combinations of supplements (vitamins, minerals and other co-factors) in a wide variety of combinations have been recommended. Among the most useful is one supporting mitochondrial function – N-acetyl-l-carnitine, co-enzyme Q10, niacin, ribose and magnesium. A more complex mixture of potent antioxidants is being trialled in the USA.5

An important question about the testing of adults for environmental chemical contamination is:

Could we be trying to correlate exposure and effect at the wrong time? If it is prenatal, or early life stage, exposure that is critical to disease susceptibility, why are we measuring environmental chemicals in people once they have developed breast cancer? The critical exposure window may have been much earlier.176

This underlines the urgency to recognize many chemicals as major developmental hazards, which must be addressed at the earliest possible moment in order to avoid longer-term and adverse consequences.

POLITICAL, SOCIAL AND MEDICAL ACTION

The response of governments, global corporations, industry and society to the accumulating evidence of the hazards of chemical contamination has been to minimize the observed effects, to accuse the scientists involved of poor science,73 scare-mongering,161,179 unrealistic attitudes180 and, in a number of extreme cases, vilification and character assassination.181,182 Government activities and research funding have been dictated by policy and not open, independent, transparent science. In an article that called for research, not propaganda, the reluctance of the medical establishment to embrace change was challenged. US Representative and physician Dave Weldon said:

Mind you, half of Dr. Wakefield’s theory has been proven correct and accepted in the medical community. Hundreds of children with regressive autism and GI [gastrointestinal] dysfunction have been scoped and clinicians are seeing the inflammatory bowel disease he first described. The NIH [National Institutes of Health] is finally funding an attempt to repeat Dr. O’Leary’s findings of measles RNA in Wakefield’s biopsy specimens, though I am disappointed it has taken this long.
A similar story is described by Arpad Pusztai, whose work upset the establishment’s ideological commitment to GM crops and food. Evidence has been sought to support policy rather than to design policy in response to medical and scientific evidence. Disturbing scientific and medical studies are being denied rather than replicated in order to establish their validity.

The failure of government and regulators to act on a report on food colouring and ADHD in this matter is regrettable and symptomatic of the unwillingness to make changes in our chemical environment that are resisted by the industry, even in the light of good science. Both the Food Standards Agency (FSA) and the European Food Standards Agency refused to endorse the precautionary principle and withdraw the products immediately.

The phthalates reveal a similar story. These were banned in some countries from 1977, but in the USA the toy industry launched strong resistance to a ban in America. One study reports a positive association between urinary phthalate metabolites and adult male (age 20–59 years) obesity. There were other positive associations with adverse health effects among young women and elderly people, but not in children.

The attitude to xenobiotics in the environment is reminiscent of the fight against tobacco and smoking. It seems that many people and organizations are prepared to sacrifice the health of present and future generations in order to make a fast buck or allow national tax income to be protected.

GULF WAR SYNDROME/ILLNESS

In November 2008, a second report on GWI was released by the Congressionally mandated Research Advisory Committee on Gulf War Veterans’ Illness (RACGWVI). The 450-page report with some 1800 references validates the earlier conclusions of the 2004 report and states:

The illnesses suffered by veterans were a result of unique circumstances in which they were exposed to a considerable number of toxic insults. The most important of these were:

- receiving multiple vaccines, some experimental;
- pyridostigmine bromide, also experimental, in Nerve Agent Pre-treatment Set (NAPS) tablets;
- pesticides, especially organophosphates, used to keep down disease vectors;
- exposure to low levels of chemical warfare agents in the form of nerve agents.

GWI has the following features:

- It is a chronic multi-system physical medical condition with a coherent pattern of symptoms.
- Many veterans show evidence of physical brain injury in the form of neuropsychological impairment, which cannot be detected by routine tests.
- It is not a stress-related condition.
- There is a twofold increase in motor neuron disease and brain cancer in people with GWI.

CONCLUSIONS

MCS is a medical, scientific, political, legal and social issue that needs to be addressed within our society as a matter of urgency. It is now beyond argument that xenobiotics have the potential to damage present and future generations.

The role of psychiatry is to embrace the science and medicine that provide the evidence of chemical and environmental damage and to support those people who have to cope with this condition.

The role of industry, science and medicine is to carry out comprehensive and independent chemical, toxicological, pharmacological and clinical studies to ensure that all products in the marketplace are safe for widespread use in the community. All data should be available for examination in the same way that scientific papers are scrutinized before publication by independent scientists and clinicians. Vested interest should have no part in this process.

The role of politics is to protect its citizens with independent funding, coupled with robust and clear regulations, without any influence from vested interests that pay thousands of pounds in lobbying fees to exert control over the political process.

Where people are physically, chemically or biologically exposed to any hazard and develop MCS and related conditions, their welfare should be put first and every provision made to ensure that they have the resources required to cope with the environment of the twenty-first century.

KEY POINTS

- MCS is a complex, chronic multi-system condition.
- It is associated with exposure to a wide variety of novel chemicals, environmental, agricultural and dietary.
- It requires a much more responsible and careful assessment and regulation of all novel chemicals in line with the precautionary principle.
- It requires recognition of the new understanding emerging from recent studies in toxicology, metabolism, genetics, epigenetics and developmental biology.
- Recognition of the condition by clinicians, education, health authorities and government authorities is required for effective treatment, the most important of which is the removal of incitants and the provision of a clean and controlled living environment.
- Research is needed in order to establish other treatments that may help at various stages of the condition.
- There may be a need for subgrouping of people with MCS.
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Multiple chemical sensitivity


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