Chapter XX

Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms

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CONTENTS

XX.1 INTRODUCTION TO MULTIPLE CHEMICAL SENSITIVITY (MCS)

Multiple chemical sensitivity (MCS) is a complex disorder with cases often apparently initiated by chemical exposure. Following initiation of illness, people with MCS report sensitivity or intolerance to low levels of a wide spectrum of chemicals. The reported symptoms of chemical exposure are diverse and variable from one patient to another, but include pain, especially headache pain, muscle and joint pain, confusion, cognitive dysfunction, asthma-type symptoms, rhinitis, sleep disturbances, fatigue and even such psychiatric symptoms as anxiety and depression and infrequently rage. In the Sorg (1999) review, a total of 41 different symptoms are listed, many of which occur only in a minority of sufferers. Among the more common symptoms following chemical exposure in MCS patients are extreme fatigue, headache, gastrointestinal problems, dizziness, anxiety, depression, upper airways irritation, muscle and joint pain, and memory and concentration difficulties (Sorg, 1999). It should be noted that six out of nine of these symptoms can probably be ascribed to central nervous system (CNS) changes. Changes in brain function have been shown in brain positron emission tomography (PET) scan studies of MCS patients (Heuser and Wu, 2001; Hillert *et al*., 2007), single photon emission computed tomography (SPECT) scan studies (Simon *et al*., 1994; Heuser *et al*., 1994; Fincher *et al*., 1997a; Fincher *et al*., 1997b) and electroencephalography (EEG) studies (Bell *et al*., 1999b; Muttray *et al*., 1995; Ross *et al*., 1999; Schwartz *et al*., 1994; Fernandez *et al*., 1999; Lorig *et al*., 1991; Lorig, 1994). Miller (2001) listed 74 such symptoms that she divided into neuromuscular, head-related, musculoskeletal, gastrointestinal, cardiac, affective, airway, cognitive and other. It is likely, as is discussed below, that the profound variation in symptoms, both qualitative and quantitive among sufferers, may be due to a local mechanism whose tissue distribution may vary among different sufferers.

MCS has been given a number of different names, including chemical sensitivity, multiple chemical sensitivities, chemical intolerance and toxicant-induced loss of tolerance (TILT). The TILT name (Miller, 2001) emphasizes the observation that most cases of MCS follow exposure to one or more chemicals and the basic hypothesis that dominates much of this literature is that chemical exposure initiates cases of illness (Ashford and Miller, 1998). The Cullen case definition requires such an initiating exposure for a case to be considered to be MCS (Cullen, 1987). Furthermore, the spectrum of chemicals reported to initiate cases of MCS is similar or identical to the spectrum of chemicals to which people with MCS appear to be sensitive, suggesting that the mechanism of action of both initiating chemicals and those eliciting sensitivity responses may be similar or identical. Some researchers, mainly those who have advocated some type of psychogenic cause for MCS, have advocated calling it idiopathic environmental intolerance (IEI) and have questioned whether chemicals are in fact initiators of MCS cases.

The phenomenon of MCS has been often ignored in the toxicological literature, largely because up until recently, a series of challenging questions about MCS have been unanswered. From a toxicological perspective, the most relevant such questions include the following:

- How can such diverse chemicals be implicated in initiating cases of MCS and, having initiated sensitivity, subsequently produce responses at very low exposures?
- How can one produce high-level sensitivities to such a broad range of chemicals, with many MCS patients being estimated as being on the order of 1000-fold more sensitive than normal?
- Are there plausible physiological mechanisms that may be expected to produce the above-described pattern of sensitization?
- If so, is there any evidence supporting these mechanisms in MCS?

I will discuss each of these four questions in this review, as well as at least eight other, perhaps equally puzzling, questions about MCS.

XX.2 DIVERSE CHEMICALS ARE REPORTED TO APPARENTLY INITIATE CASES OF MCS

There have been dozens of papers reporting a pattern of chemical exposure preceding development of cases of MCS, typically one high-level exposure or multiple

lower-level exposures (Ashford and Miller, 1998; Sorg, 1999). Pall (2007a, Chapter 13) cited 24 distinct studies reporting chemical exposure preceding development of many cases of MCS and Miller (2000) cited 12 additional such studies and still additional studies are cited below in this section. The types of chemicals most commonly involved are the volatile organic solvents (sometimes described as volatile organic compounds (VOCs)) and pesticides, especially organophosphorus and carbamate pesticides (Ashford and Miller, 1998; Sorg, 1999; Rea, 1992; Ziem and McTamney, 1997). There are a number of additional papers reporting that exposure to organic solvent chemicals that outgas in 'sick building syndrome' situations also appear to initiate cases of MCS (Welch and Sokas, 1992; Davidoff and Keyl, 1996; Miller *et al*., 1999; Hodgson, 2000; Arnold-Llamosas *et al*., 2006; Redlich *et al*., 1997; Ross, 1997). Berglund *et al*. (1984) reported that apparently chemically sensitive individuals reacted to air piped in from such a 'sick building' in blinded fashion, but did not react to uncontaminated air, suggesting that chemicals in the 'sick building' air were causal in generating the reactions. Many of the chronic symptoms of the surviving victims of the Bhopal disaster may be ascribed to MCS (Ross, 2000; Nemery, 1996).

When Miller and Mitzel (1995) wanted to compare cases of MCS apparently initiated by two different classes of chemicals, they chose cases from recently remodelled sick buildings (volatile organic solvent exposure) and compared those with cases apparently initiated by organophosphorus pesticides. In their highly cited paper, Miller and Mitzel (1995) found these two groups of MCS patients were similar, but not identical to each other, with some differences in symptom patterns and some differences in average severity between the two groups. Because MCS cases apparently initiated in these two ways are so common, it was relatively easy for Miller and Mitzel to find substantial numbers of patients of the two types to study.

Two of the most interesting sick-building cases occurred in the then recently remodelled Environmental Protection Agency building in Washington DC, in which approximately 200 people were apparently sickened with cases of MCS (Miller, 2001) and in Brigham and Women's Hospital in Boston, part of the Harvard Medical School complex. The latter case was described in detail in a US government publication (Kawamoto *et al*., 1997), where subsequent decreases in chemical usage and increases in air flow led to substantial decreases in new cases of chemical sensitivity and related illnesses, suggesting a causal relationship between chemical exposure and illness initiation. Ashford and Miller (1998) suggested that the decreases in required air flow in buildings in the USA, as a response to the energy crises of the 1970s, led to major increases in the incidence of MCS. In an important study, occupational medicine patients differed from general patients in responses to the Toronto MCS questionnaire in much the same way that self-identified MCS patients did, albeit to a lesser extent (McKeown-Eyssen *et al*., 2001), suggesting that chemical exposure in the occupational environment may initiate substantial numbers of MCS cases. Zibrowski and Robertson (2006) reported increased prevalence of MCS-like symptoms among laboratory technicians exposed to organic solvents, as compared with similar laboratory technicians with no apparent exposure. An epidemiological study, estimating the prevalence of MCS in various occupations, including those expected to have substantial chemical exposure to classes of chemicals implicated in MCS as a consequence of the occupation, reported increased prevalence of MCS in several occupations involving such chemical exposure, again suggesting a causal role of chemical exposure (Maschewsky, 1996; Maschewsky, 2002). Yu *et al*. (2004) found high prevalences of MCS-like symptoms among solvent-exposed printing workers, as compared with non-chemically exposed controls. There are at least a dozen studies reporting high prevalences of reactive airways disease, a common aspect of MCS, among workers occupationally exposed to organic solvents.

In addition to organic solvents and related compounds and the organophosphorus and carbamate pesticides, there are additional classes of chemicals that are reported to apparently initiate cases of MCS. These include the organochlorine pesticides chlordane, lindane, dieldrin and aldrin (Corrigan *et al*., 1994; Ziem and McTamney, 1997; Lohmann *et al*., 1996; Wallace, 1995; Pröhl *et al*., 1997) and also a variety of pyrethroid pesticides (Corrigan *et al*., 1994; Lohmann *et al*., 1996; Altenkirch, 1995; Altenkirch *et al*., 1996. Lindane has been shown to initiate animal models of MCS (Gilbert, 2001; Cloutier *et al*., 2006) as has another $GABA_A$ (γ-aminobutyric acid A receptor) antagonist (Adamec, 1994). There are reports that hydrogen sulfide exposure can initiate cases of MCS-like illnesses (Kilburn, 1997; Kilburn, 2003). Donnay (1999; 2000) has reviewed evidence suggesting that carbon monoxide exposure may be able to initiate cases of MCS. Furthermore, mercury and mercurial compounds are also reported to apparently initiate some cases of MCS (Eneström and Hultman, 1995; Latini *et al*., 2005; Brent, 2001; Stejskal *et al*., 1999) and dental assistants working with mercury amalgams were reported to have higher prevalences of neurological symptoms including MCS-like symptoms (Moen *et al*., 2008).

Mould exposure is also suggested to initiate cases of MCS in sick-building situations characterized by mould-infested buildings (Redlich *et al*., 1997; Claeson *et al*., 2002; Lee, 2003; Mahmoudi and Gershwin, 2000; Straus *et al*., 2003). Here, we cannot say much about what mycotoxins may be involved, although there is some evidence that *Stachybotrys* moulds may be often involved (Mahmoudi and Gershwin, 2000; Hintikka, 2004; Straus *et al*., 2003; Pestka *et al*., 2008). Hirvonen *et al*. (1999) reported that mouldy 'sick' buildings

produced increases in nitric oxide (NO) and inflammatory cytokines in nasal passages of exposed people and similar responses were also reported in the lungs of similarly exposed people (Akpinar-Elci *et al*., 2008). NO and inflammatory cytokines are important aspects of the MCS mechanism developed in this review.

XX.3 A COMMON RESPONSE TO INITIATING CHEMICALS: INCREASED NMDA ACTIVITY

One of the great puzzles about MCS is how can such a diverse group of chemicals produce a common biological response? In fact, one of the MCS skeptics, Ronald Gots (1996) has argued that MCS cannot possibly be a physiological response to chemicals because the diverse chemicals implicated in MCS cannot possibly produce a common response in the human body. Clearly one needs to find such a common physiological response in order to develop a compelling model of the mechanism of MCS. An important role for excessive NMDA (*N*-methyl-D-aspartate) receptor activity in MCS was first suggested by Thomas (1998) and by Dudley (1998). Pall (2002) argued that elevated NMDA[a] receptor activity is likely to have a key role in MCS and that chemicals were likely to act, in most cases indirectly, to increase such activity. There were several types of evidence reviewed in that paper suggesting a role of elevated NMDA activity:

1. MCS patients are hypersensitive to monosodium glutamate and glutamate is the common physiological agonist of the NMDA receptors.
2. In studies of the genetic polymorphism of the CCK-B gene, the allele of the gene that acts indirectly to produce higher NMDA activity was associated with increased prevalence of MCS (Binkley *et al*., 2001; see Pall, 2002 for discussion).
3. The NMDA antagonist, dextromethorphan was reported from both clinical observations and anecdotal reports to lower reactions to chemicals in MCS patients.
4. Bell and others have proposed that neural sensitization has a key role in MCS and the probable mechanism for such neural sensitization, called long-term potentiation (LTP), is known to involve increased NMDA activity.
5. Elevated NMDA activity has been shown to play an essential role in several animal models of MCS.
6. Elevated NMDA activity appears to play a role in such related illnesses as fibromyalgia (FM), chronic fatigue syndrome (CFS) and post-traumatic stress disorder (PTSD), with the most extensive evidence for such a role being found in FM (Pall, 2006; Pall, 2007a).

It should be noted that numbers 2 and 5 above suggest that chemicals initiating cases of MCS may act to increase NMDA activity and number 3 suggests that chemicals acting in those already sensitive may also act to increase NMDA activity. In fact, these two sets of chemicals are similar or identical to each other (Ashford and Miller, 1998) so it should not be surprising if they both may act via the same mechanism(s). All of these considerations raise the question about whether there are known mechanisms by which the several classes of chemicals implicated in MCS may act to increase NMDA activity?

XX.3.1 Pesticides and NMDA Stimulation

In that Pall (2002) review, evidence was discussed showing that organophosphorus and carbamate toxicants (including pesticides) can act to produce increases in NMDA activity via the following pathway: these toxicants are acetylcholinesterase inhibitors, producing an increase in acetylcholine, which stimulates the muscarinic receptors, which produce, in turn, increased glutamate release leading to increased NMDA receptor stimulation, as well as stimulating other glutamate receptors (see diagram in **Figure 1**). There are a large number of studies showing that toxic effects of organophosphorus toxicants in mammals can be greatly lowered by using NMDA antagonists (Dekundy *et al*., 2007; Lallement *et al*., 1998; Martin and Kapur, 2008), showing that such increased NMDA activity has a substantial role in producing the response to these toxicants.

What about other pesticides and other groups of implicated chemicals? Let us take the different classes of chemicals one at a time. The organochlorine pesticides, chlordane, lindane, dieldrin and aldrin have all been shown to lower $GABA_A$ receptor activity (Gant *et al*., 1987; Corrigan *et al*., 1994; Cassidy *et al*., 1994; Brannen *et al*., 1998; Narahashi *et al*., 1995) and this, in turn is well known to produce elevated NMDA activity (Blaszczak and Turski, 1998; Watanabe *et al*., 1995; Tusell *et al*., 1992), see **Figure 1**. In fact these same citations show that seizure activity produced by these $GABA_A$ antagonists, including these pesticides, is lowered or blocked by NMDA antagonists, showing that the elevated NMDA activity produced by such toxicants has a key causal role in the mechanism of seizure generation. Because MCS involves the action of short-term stressors producing chronic illness, it may be of special interest that this pathway produces chronic changes in brain function that can be blocked by short-term interruption of the pathway (Kaindl *et al*., 2008).

Pyrethroid pesticides, which also initiate cases of MCS, act to produce long-term sodium-channel opening (Narahashi *et al*., 1995; Valentine, 1990; Wu and Liu,

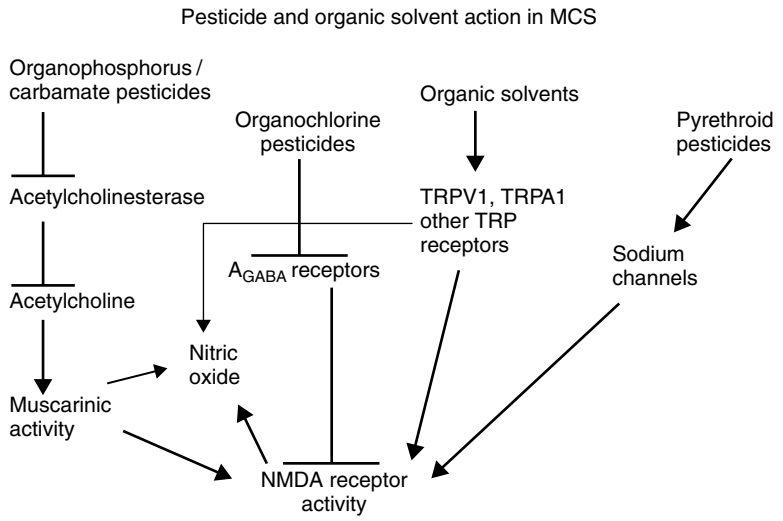

Figure 1. Pathways for action of pesticides and organic solvents. Each chemical class implicated in the initiation of cases of MCS can act along a distinct pathway to generate increases in NMDA activity, as shown in the figure. Each arrow represents a mechanism by which one parameter stimulates another. Some inhibitory (negative) interactions are also indicated. Both the organophosphorus/carbamate toxicants and the organochlorine pesticides have doubl- negative interactions. Such negative interactions, together with the arrows in the figure, indicate that the each of the four classes of compounds acts along one of these pathways, leading to an increase in NMDA activity

2003; Bradberry *et al*., 2005; Proudfoot, 2005). This in turn, produces increased NMDA stimulation (Wu and Liu, 2003; Yu, 2006; Doble, 1996), see **Figure 1**. Type II pyrethroids also act as $GABA_A$antagonists (Valentine, 1990) and may be expected, therefore, to also act along the same pathway impacted by the organochlorine pesticides, and thus lead to increased NMDA activity along that pathway as well.

XX.3.2 Organic Solvents, TRP Receptors and NMDA Stimulation

Clearly the greatest puzzle of chemical activity in MCS is how does the huge family of organic solvents act to initiate cases of MCS or elicit sensitivity symptoms in those who have become sensitive? These chemicals are the predominant set of chemicals that trigger reactions on a day-to-day basis in MCS patients. They have also been referred to as volatile organic chemicals and yet it is clear that nonvolatile chemicals ingested or absorbed through the skin can produce reactions, so the volatility is important due to the most common mode of exposure, inhalation, rather than being an essential part of the mechanism of sensitivity. I will refer to this extremely large group of chemicals as organic solvents, even though that does not cover this entire spectrum of chemicals.

Pall and Anderson (2004) argued that the probable target for such organic solvents in MCS is the vanilloid (transfer receptor potential (TRP)V1) receptor, and presented 12 distinct types of evidence arguing for such a TRPV1 role in MCS. That paper was extensively documented with 222 citations and while specific references are provided some of this discussion, for the rest the reader is referred back to that paper. One type of evidence that we presented is that some solvents well known to be involved in MCS, such as formaldehyde and other aldehydes, were quite active TRPV1 agonists, and a variety of alcohols are vanilloid agonists and may be converted into still more active aldehydes via alcohol dehydrogenases in the body. It is known that capsaicin, the classic TRPV1 agonist, requires both hydrophobic regions and a hydrogen-bonding group in order to act as an agonist, suggesting that strictly hydrophobic solvents might require cytochrome P450 metabolism in order to act as a vanilloid agonist, or might act synergistically with a solvent that does have a hydrogen-bonding group. There is evidence from animal models of MCS, which are also animal models of Gulf War illness, for such synergistic interactions of organic solvents and related compounds (Research Advisory Committee on Gulf War Veterans Illnesses., 2004): fully 28 studies of synergistically acting stressors, most, but not all, of which were organic compounds, were reviewed in that document.

Some mycotoxins are known TRPV1 agonists, so it is possible that the role of moulds in MCS may be explained through the role of the TRPV1 receptor. Chemical sensitizers, including toluene diisocyanate (TDI) and eugenol, which produce local sensitivity to a wide range of chemicals, are known TRPV1 agonists. MCS patients often report sensitivity to chlorine gas from swimming pools or from drinking water, and chlorine acts as a TRPV1 agonist *in vivo* (Morris *et al*., 2005), producing

an irritant response. TRPV1 stimulation produces neurogenic inflammation and also reactive airways disease (Geppetti *et al*., 2008; Jia and Lee, 2007; Planells-Cases *et al*., 2005; Costa *et al*., 2008), often called reactive airways dysfunction syndrome (RADS), a form of asthma showing reaction to a spectrum of chemicals similar or identical to those involved in MCS. Both RADS and neurogenic inflammation are often aspects of MCS cases (Meggs, 1994; Meggs, 1997).

Millqvist and her colleagues have published a series of papers showing that MCS patients are hypersensitive to capsaicin, the classic TRPV1 agonist, again providing support for a TRPV1 role in MCS (Johansson *et al*., 2002; Millqvist, 2000; Ternesten-Hasséus *et al*., 2002; Millqvist *et al*., 2005; Millqvist *et al*., 2008). Many studies have shown that capsaicin treatment leads the TRPV1-stimulated cells in several regions of the body to release glutamate neurotransmitter, leading in turn to NMDA stimulation (10 such studies are cited in Pall and Anderson, 2004). These studies provide further support for the contention that each class of chemicals involved in MCS leads to increased NMDA stimulation.

There is an additional parallel between MCS and TRPV1 stimulation. MCS patients have a phenomenon known as desensitization or masking, such that low-level chronic or repeated chemical exposure leads to decreased reactivity to chemical exposure (Ashford and Miller, 1998). This may be the basis of using low-level chemical exposure to treat MCS patients (Weaver, 1996; Rea, 1997). Low-level chronic or repeated exposure to many TRPV1 agonists leads to lowered TRPV1 activity through a complex series of changes involving increased intracellular calcium levels, complex protein phosphorylation control and probably receptor internalization (Szallasi and Blumberg, 1999; Itagaki *et al*., 2004). Thus the desensitization/masking phenomenon found in MCS may be produced, to part or in whole, by this lowered TRPV1 activity.

While there are many properties suggesting a TRPV1 role in MCS, it is clear now that some of the interpretations given by Pall and Anderson (2004) to some of the relevant data were too narrow. It was argued, for example, that TRPV1 was primarily responsible for the sensory irritation (SI) response, a response elicited by chemicals including alkanes, alkyl benzenes, halogenated benzenes, halogenated alkylbenzenes, alcohols, ketones, ethers, aldehydes, formaldehyde, isocyanates and chlorine (Nielsen, 1991; Alarie *et al*., 1998; Inoue and Bryant, 2005; Cometto-Muñiz and Abraham, 2008), a broad range of chemicals also implicated in MCS. It is now clear that this SI response involves as major players, other members of the TRP family of receptors, not just TRPV1. Specifically Bíró *et al.* (2007) discuss evidence for a role of TRPA1, TRPM8 and TRPV2, 3 and 4 receptors in this response, as well as TRPV1. Bautista *et al.* (2006) implicated specifically the TRPA1 receptor in the response to several environmental irritants. Many of the TRP receptors have roles in responding to xenobiotics (Nilius, 2007) and while our knowledge of such roles has been expanding rapidly in recent years, it is still, no doubt, incomplete. Neurogenic inflammation and reactive airways disease aspects of MCS, discussed above and below, are produced, not only through TRPV1 stimulation, but also through the action of other TRP receptors (Geppetti *et al*., 2008; Jia and Lee, 2007). Whereas some chemical sensitizers act as TRPV1 agonists, sensitizers can also act as TRPV3 agonists (Xu *et al*., 2006).

Others have argued for a central role for the SI response and the receptors involved in that response in MCS (Skov and Valbjorn, 1987; Meggs, 1993; Meggs, 1997; Anderson and Anderson, 1999a; Anderson and Anderson, 1999b; Anderson and Anderson, 2003; Millqvist *et al*., 1999; Millqvist, 2000; Millqvist, 2008; Nordin *et al*., 2005).

In Pall and Anderson (2004), we used the desensitization response produced by low-level chronic exposure to capsaicin or other bona fide TRPV1 agonists to assess whether some solvents that had never been tested as possible TRPV1 agonists might have such activity. The reasoning was that if responses to a chemical were reported to be substantially reduced after low-level capsaicin treatment, that chemical should be labelled as a probable TRPV1 agonist, because the response to it was lowered along with TRPV1 desensitization. It is clear now that desensitization of one TRP receptor is often accompanied by desensitization of others. For example, TRPV1 and TRPA1 can undergo cross-desensitization (Rohacs *et al*., 2008; Ruparel *et al*., 2008) and TRPM8 and TRPA1 desensitization can also be produced in parallel (Zanotto *et al*., 2008). In another study, a series of TRPC receptors were desensitized together by a receptor internalization process (Itagaki *et al*., 2004). It seems likely, therefore, that some organic solvents that were argued to be probable TRPV1 agonists, as suggested earlier in this paragraph, may well be agonists of other TRP family receptors.

Of the other TRP family receptors, the one most likely to have a substantial role in MCS, based on current evidence, is TRPA1. TRPA1 is responsible for the activity of a number of different sensory irritants (Bautista *et al*., 2006; Gerhold and Bautista, 2008), with TRPV1 being responsible for others. For a number of such irritants, the chemicals react by reversible covalent modification with the TRPA1 receptor (Hinman *et al*., 2006). Among the TRPA1 agonists are certain aldehydes, including acrolein and aldehydic components of cigarette smoke (Andrè *et al*., 2008; Simon and Liedtke, 2008) and MCS patients are commonly known to be sensitive to cigarette smoke. Formaldehyde which is commonly involved in initiating cases of MCS was shown in a recent study to act via the TRPA1 receptor in a model of inflammatory pain, rather than acting via the TRPV1 receptor (McNamara *et al*., 2007).

Activation of the TRPA1 receptor has been reported to lead to the release of the neurotransmitter glutamate, leading in turn, to increased NMDA activity (Kosugi *et al*., 2007; Ding *et al*., 2008). Given that such increased NMDA activity is also produced by TRPV1 receptor stimulation, as discussed above, it should not be surprising that organic solvent-produced changes in the nervous system can, in many cases, be blocked or lowered by using NMDA antagonists. For example, there are a number of responses to formaldehyde exposure that have been shown to be greatly lowered by NMDA antagonists (Coderre and Melzack, 1992; McMahon *et al*., 1993; Wiertelak *et al*., 1994; Wang *et al*., 1999).

In conclusion, there are compelling similarities between the diverse organic solvents and related chemicals involved in MCS and the diverse organic chemicals involved in the SI response. It seems likely that the TRP receptors are involved in both, with the two most likely members of this receptor family to be involved in chemical responses in MCS and in SI, based on current evidence, being the TRPV1 and TRPA1 receptors, both of which can produce an increase in glutamate release and consequent NMDA stimulation. These various data suggest, therefore, that the proposed pattern of chemical involvement in MCS acting through increased NMDA activity is likely to be sustained for the organic solvent group of chemicals.

Before leaving this issue of the apparent roles of TRP receptors in MCS, I need to discuss the TRPM2 receptor that may have a role in amplifying responses in MCS. The TRPM2 receptor is known to be stimulated by oxidants, including hydrogen peroxide, with much of the stimulation being produced by adenosine diphosphate (ADP)-ribose, a signalling molecule whose levels can be greatly increased by oxidants (Kühn *et al*., 2005; Fonfria *et al*., 2004; Wilkinson *et al*., 2008; Naziroglu, 2007; Buelow *et al*., 2008; Lange *et al*., 2008). The pathway of synthesis of poly(ADP)-ribose is as follows: oxidants produce nicks in DNA strands in the nucleus of cells which can lead, in turn, to a massive stimulation of poly(ADP)-ribose polymerase activity, producing poly(ADP)-ribosylation of chromosomal proteins. When this poly(ADP)-ribose becomes subsequently hydrolysed, it produces free ADP-ribose which acts as a signalling molecule. One oxidant that is very active in this process is peroxynitrite ($ONOO^-$) (Pacher and Szabo, 2008), a molecule that the author has argued (see below) has a key role in MCS and related illnesses, and whose synthesis is greatly increased by NMDA stimulation (reviewed in Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003). Consequently, TRPM2 activity is predicted to be elevated in MCS and to be stimulated by chemical exposure. TRPM2 may both directly and indirectly leading to increases in NO and $ONOO^-$ production, thus amplifying the already elevated levels of these compounds (see Yamamoto *et al*., 2008 for discussion). There is some evidence that another TRP receptor, TRPM7, may also have a role in this process (Miller, 2006). The role of TRPM2 and possibly 7 may be one of several interacting mechanisms that may lead to the extraordinary chemical sensitivity reported in MCS patients.

There is evidence that other TRP receptors are elevated in response to oxidants and products of oxidative stress biochemistry, including TRPV1 and TRPA1 (Taylor-Clark *et al*., 2008; Bessac *et al*., 2008; Andersson *et al*., 2008; Trevisani *et al*., 2007; Puntambekar *et al*., 2005; Schultz and Ustinova, 1998; Ustinova and Schultz, 1994), but these effects may be more modest than those on TRPM2. The effects on TRPV1 receptors makes them more susceptible to stimulation by their effectors, whereas with TRPM2, oxidative stress acts to open the receptor channel independently of any effector and so may produce a greater physiological response under many circumstances.

XX.3.3 Other Apparent Initiators and Summary of NMDA Role

Three other apparent initiators of cases of MCS were discussed above, carbon monoxide, hydrogen sulfide and mercury. Do any of these act to increase NMDA activity?

Carbon monoxide has been reported to produce such increased NMDA activity and NMDA antagonists block or lower the toxic responses to carbon monoxide exposure (Thom *et al*., 2004; Liu and Fechter, 1995; Penney and Chen, 1996; Ishimaru *et al*., 1992). Hydrogen sulfide can also produce increased NMDA activity and again its toxic effects are lowered by NMDA antagonists (Cheung *et al*., 2007; Qu *et al*., 2008; Kamoun, 2004). Mercury, acting through its metabolic product methylmercury, also acts to produce increases in NMDA activity, and again methylmercury toxicity is lowered by NMDA antagonists (Juárez *et al*., 2005; Allen *et al*., 2002; Faro *et al*., 2002; Miyamoto *et al*., 2001; Zhang *et al*., 2003; Rossi *et al*., 1997). Methylmercury acts to produce such increased NMDA activity, at least in part, by lowering the transport of the glutamate, the most important physiological NMDA agonist (Juárez *et al*., 2005; Allen *et al*., 2002).

In summary, then, we have evidence that all seven classes of compounds reported to initiate cases of MCS can each act to increase NMDA activity (**Figure 1**). At least for some members of each class under some conditions, NMDA antagonists can lower the toxic responses to each of them. While evidence linking any one of these to increased NMDA activity may be coincidental, the pattern of evidence for all seven strengthens the argument that increased NMDA activity is not likely to be coincidental. When coupled to the six types of additional evidence, discussed at the beginning of this section, on the apparent NMDA role in MCS, one can argue that there is very substantial evidence, not only that increased

NMDA activity has a role in MCS, but also that chemicals are likely to act indirectly by increasing such NMDA activity.

There is extensive evidence that increased NMDA activity produces increases in NO and also its oxidant product $ONOO^-$ (reviewed in Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003), and it will be argued below that all three of these, NMDA activity, NO and $ONOO^-$, are likely to have key roles in MCS.

XX.4 GENETIC EVIDENCE FOR CHEMICAL EXPOSURE BEING CAUSAL IN MCS

The pattern of chemical exposure preceding cases of MCS and the common mode of action of these chemicals in increasing NMDA activity strongly suggests causality of those exposures. However, one would like to have independent confirmation of causality. Such independent confirmation has come from genetic studies of susceptibility to MCS. There have been three such studies, each providing evidence that chemicals have causal roles in initiating cases of MCS (summarized in **Table 1**).

The first of these to be published was a study by Haley *et al*. (1999) on Gulf War veterans, including those suffering from what some have called Gulf War syndrome. There are several reports that the Gulf War syndrome veterans suffer from MCS or an MCS-like illness (Proctor *et al*., 2001; Reid *et al*., 2001; Miller and Prihoda, 1999; Thomas *et al*., 2006) and there is also evidence that they suffer from such related illnesses as CFS and FM (Chapter 10 in Pall, 2007a; Pall, 2001a). The Gulf War veterans were exposed to over a dozen stressors that may have had a role in initiating their illnesses (Chapter 10 in Pall, 2007a), one of which was exposure to the organophosphorus toxicants, sarin and cyclosarin, which are both potent inhibitors of acetylcholinesterases. What Haley *et al*. (1999) report is that those carrying a form of the gene for PON1 that makes them less able to metabolize these neurotoxicants, were more susceptible to developing the neurological symptoms that comprise Gulf War syndrome. This provides substantial evidence that sarin/cyclosarin had a causal role in initiating cases of Gulf War syndrome and that those less able to detoxify these toxicants were therefore more susceptible to it. Mackness *et al*. (2000) showed that British Gulf War veterans with self-reported Gulf War syndrome tended to have lowered activity for the enzyme encoded by the PON1 gene, the paraoxonase enzyme, suggesting again a link to the organophosphorus toxicants. However, in this case, the low activity was not shown to be caused by the genetic polymorphisms of the PON1 gene, so the argument for causality is weaker than in the Haley *et al*. (1999) study. Another study from the same group (Mackness *et al*., 2003), showed that among farmers using sheep dip containing an organophosphorus pesticide, farmers reporting chronic ill health tended to carry the the PON1 allele that produces lowered metabolism of that pesticide, as compared with farmers reporting good health. Unfortunately, MCS prevalence in these two groups of farmers was not studied.

Two studies somewhat similar to the Haley *et al*. (1999) study have been done, comparing a large number of civilian MCS sufferers with unaffected controls (**Table 1**). One was the Canadian study by McKeown-Eyssen *et al*. (2004) and the second, the German study by Schnakenberg *et al*. (2007). Each of these showed that three distinct polymorphic genes involved in the metabolism of chemicals otherwise implicated in initiation of MCS cases have a statistically significant influence on susceptibility (**Table 1**). In the Schnakenberg *et al*. (2007) study, there was an extremely high level of statistical significance for each of these three genes, so that the probability of getting these results by chance if there is no true correlation is less than one in 10^{11}. In total, in these three studies (Haley *et al*., 1999; McKeown-Eyssen *et al*., 2004; Schnakenberg *et al*., 2007), five genes which help determine the rate of metabolism of chemicals previously implicated in MCS have been found to have statistically significant association with the prevalence of MCS; a sixth genetic polymorphism, for the gene GSTT1 had a statistically significant effect only in conjunction with specific alleles of other implicated genes (**Table 1**). A recent similar, but much smaller study, roughly one quarter of the size of the McKeown-Eyssen *et al*. (2004) study and one ninth the size of the Schnakenberg *et al*. (2007) study, failed to find any statistically significant differences between apparent cases and controls (Wiesmüller *et al*., 2008). Of the three larger studies, we have a pattern of evidence showing that genes that metabolize chemicals otherwise implicated in MCS initiation, have substantial influence on the susceptibility to develop MCS. These results support the inference that chemicals acting as toxicants cause many cases of MCS and that those chemicals must be in their toxic form in order to so act. Therefore, alleles of polymorphic genes that either decrease or increase the metabolism of these chemicals will influence the susceptibility to MCS.

One point that should be emphasized is that genetic studies of this type may well give different results with different populations, because populations may differ in either chemical exposure or in the frequencies of the polymorphic alleles in their gene pools. The genetic roles presumably involved here are what are often described as environment X gene interactions. An apparent example of this comes from studies of autism susceptibility where the susceptibility to autism in the USA and Romania, but not in Italy was apparently influenced by the PON1 gene (Pasca *et al*., 2006; D'Amelio *et al*., 2005). The differences were ascribed to the much higher use of organophosphorus pesticides in the USA and Romania than in Italy (Deth *et al*., 2008).

Table 1. Genetic polymorphisms influencing MCS susceptibility

Gene	Study	Function—chemical metabolism	Comments
PON1	H, M	Detoxification of organophosphorus toxicants	—
CYP2D6	M	Hydroxylation of hydrophobic compounds	Hydroxylation of compounds without hydrogen binding group may be expected to lead to greater activity as a TRPV1 agonist
NAT2	M, S	Acetylation	May produce more or less activity depending on the specific compound involved
GSTM1	S	Provide reduced glutathione for conjugation	Should increase detoxification and excretion
GSTT1	S	Glutathione conjugation	Should increase detoxification and excretion
GSTP1	S	Glutathione conjugation	Should increase detoxification and excretion; only statistically significant role was in conjunction with specific alleles of other genes

H, Haley *et al*. (1999); M, McKeown-Eyssen *et al*. (2004); S, Schnakenberg *et al*. (2007).

Are there any alternative interpretations to these genetic data, other than that the metabolism of these chemicals influences their role as toxicants in initiating cases of MCS? There is an alternative for two of the five genes, but not for the other three (**Table 1**). The gene for glutathione reductase has a very important role in the body's protective response to oxidants and oxidative stress, and the PON1 gene has a role in dealing with some of the lipid oxidation products produced by oxidative stress (Draganov and La Du, 2004), at least in lipoproteins in the blood. It follows that the roles of these two genes may be interpreted in an alternative way, but those of the other three genes cannot. The only consistent interpretation for these studies, taken as a whole, is that chemicals act as toxicants in the initiation of cases of MCS. By determining the rate of the metabolism of these chemicals, the genes help determine the incidence and prevalence of MCS.

There is strong, I would argue compelling, evidence that chemical exposure is causal in the initiation of many cases of MCS. What we need to do is to determine what physiological mechanisms are likely to be involved in such initiation. Furthermore, because low levels of similar, if not identical chemicals, trigger sensitivity responses in those already sensitive, similar pathways of action are likely to be involved in such low-level chemical responses.

XX.5 MCS DOES NOT CENTRE ON AN OLFACTORY RESPONSE

The receptors that are implicated in the response to chemicals that are discussed above are not the olfactory receptors (Axel, 2005; Buck, 2005), and yet there have been many descriptions of MCS calling it a reaction to 'odours'. There is no evidence that the olfactory system has a central role here and there is considerable evidence against such a role. Ashford and Miller (1998) reviewed a number of studies where people with severe nasal congestion still reacted to chemical exposures. There are cases of MCS in people with no sense of smell, that is people suffering from anosmia (Doty, 1994). Many MCS patients report reacting at times when they could not smell any chemical odour. There have been three studies of patients where a nose clip was used to block off access of odourants to the nasal epithelia and those MCS patients still reacted to chemical exposure (Joffres *et al*., 2005; Millqvist and Löwhagen, 1996; Millqvist *et al*., 1999). In a recent study, regions of the brain that respond to odours were found to have lowered responses to odourants in MCS patients as compared with controls, not elevated responses (Hillert *et al*., 2007). The author is not arguing that the olfactory mechanism is never impacted in MCS cases, but rather that it does not have any essential role in the chemical sensitivity process and should not be the focus of studies, when trying to assess responses of MCS patients to chemicals. We are looking at a response to chemicals, many of which have odours, not a response to odours.

XX.6 PREVALENCE ESTIMATES

Sorg (1999) reviewed prevalence studies of MCS by concluding that 'prevalence of severe MCS in the United States is approximately 4%'. She also concludes that those with milder chemical sensitivity are about 15–30% of the US population. Several more recent studies of MCS prevalence provide additional information on this issue (Kreutzer *et al*., 1999; Caress and Steinemann, 2003; Caress and Steinemann, 2004a; Caress and Steinemann, 2004b; Caress and Steinemann, 2005). Pall (2007a, Chapter 11) estimated that the prevalence of severe MCS in the USA was probably about 3.5%,

with much larger numbers, perhaps 12–25% modestly affected. These estimates are slightly lower than the Sorg (1999) estimate. There have been few studies of MCS prevalence in other countries, but one study each from Canada (Joffres *et al*., 2001), Germany (Hausteiner *et al*., 2005), Sweden (Johansson *et al*., 2005) and Denmark (Berg *et al*., 2008) suggest prevalences of roughly 50–100% of those in the USA. All of these studies suggest that there is substantial impact of MCS on public health.

Caress and Steinemann (2003) estimated that 1.8% of the entire US population have lost their jobs due to chemical sensitivity, suggesting that many of the more severely affected may be unemployed or underemployed due to their MCS. There are no similar figures with regard to housing, but anecdotal reports suggest that the most sensitive often have great difficulty finding housing they can tolerate.

XX.7 CASE DEFINITIONS

Probably the best review of and comparison of different case definitions for MCS was published by the Toronto group (McKeown-Eyssen *et al*., 2001). In that review, they compared seven different proposed case definitions, those of Randolph (1965), Cullen (1987), Thomson *et al*. (1985), the National Research Council, Board on Environmental Studies and Toxicology, Commission on Life Sciences (1992), Ashford and Miller (1998), Nethercott *et al*. (1993) and the 1999 Consensus (MCS Consensus Conference, 1999). These differ from each other in various ways, most notably in whether they require that the symptoms be polysystemic, associated with multiple organs, whether cases must be chronic, whether cases must be acquired as a consequence of one or more chemical exposure events and whether sensitivity responses must be produced by multiple 'unrelated' chemicals.

McKeown-Eyssen *et al*. (2001) compared various groups of patients with each other for their fit to each of these case definitions, using the University of Toronto Questionnaire. They compared the case definitions in several ways using this data, but perhaps the most crucial comparison was how well a specific case definition was able to discriminate between environmental practice patients and general practice patients. By that criterion, the Nethercott *et al*. (1993) case definition and the 1999 Consensus were the best, giving the highest odds ratio in comparing these groups of patients, with both giving odds ratios of roughly 20. The 1999 Consensus case definition (MCS Consensus Conference, 1999) is the one currently used on the Wikipedia site discussion of MCS and may be currently the most widely accepted case definition.

It should be noted that comparing occupational medicine practice patients with general practice patients also produced high odds ratios by these two case definitions, albeit lower ones than did the previously discussed comparison, suggesting that occupational chemical exposure often causes cases of MCS, as defined by these two case definitions (McKeown-Eyssen *et al*., 2001).

In contrast, the Cullen (1987) case definition only had an odds ratio of about eight, much lower than the Nethercott *et al*. (1993) or the 1999 Consensus case definition. The Cullen (1987) case definition has been criticized because of an additional, perhaps more important concern: it requires that 'no widely accepted test of physiologic function can be shown to correlate with symptoms'. However, as will be discussed below, there are a number of such tests that have been reported, tests of objectively measurable responses to low-level chemical exposure. This specific Cullen requirement may also be objected to, because it means, in effect, that we must stay perpetually ignorant of the aetiological mechanism of MCS. It should be discarded in the author's view, therefore, both for empirical and theoretical reasons.

There is one other issue that should be considered here, regarding what should and should not be part of an MCS case definition. Lacour *et al*. (2005) argued that only those patients who suffer from CNS-related complaints in response to chemical exposure should be considered to be true MCS patients. Such CNS-related symptoms include headache, fatigue, confusion and cognitive dysfunction. One possible rationale for this proposal is that Bell and others, as discussed below, have proposed a CNS mechanism for MCS involving neural sensitization in the brain, such that chemical exposure produces changes in synaptic sensitivities over substantial regions of the brain. Lacour *et al*. (2005) report that self-reported complaints of apparent MCS patients most commonly included CNS symptoms with symptoms derived from other regions of the body being less frequent. There is an argument for using a case definition for MCS that excludes patients without CNS-related symptoms.

Let us end this discussion by comparing the 1999 Consensus case definition (MCS Consensus Conference, 1999), listed immediately below with a couple of modifications that the author wishes to suggest for the reader's consideration:

1. Symptoms are reproducible with repeated (chemical) exposures.
2. The condition has persisted for a significant period of time.
3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (i.e. increased sensitivity).
4. The symptoms improve, or resolve completely, when the triggering chemicals are removed.
5. Responses often occur to multiple, chemically unrelated substances.
6. Symptoms involve multiple-organ symptoms.

XX.7.1 Suggestion #1

The main concern here is that it is not clear what chemically unrelated means. If it means that there is no relationship among these chemicals that can be challenged, because they all may act to produce increased NMDA activity. Describing them as being chemically diverse is more accurate. This should not change how the case definition is used in practice.

1. Symptoms are reproducible with repeated (chemical) exposures.
2. The condition has persisted for a significant period of time.
3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (i.e. increased sensitivity).
4. The symptoms improve, or resolve completely, when the triggering chemicals are removed.
5. Responses occur to multiple, chemically diverse substances.
6. Symptoms include those derived from multiple organs.

XX.7.2 Suggestion # 2

This suggestion includes the requirement for CNS involvement proposed by Lacour *et al*. (2005), and thus may correspond to what some consider to be the most classic aspect of MCS. I am sure that these two suggested case definitions will have much overlap in practice terms, because many will have symptoms derived from multiple organs, one of which is the brain.

1. Symptoms are reproducible with repeated (chemical) exposures.
2. The condition has persisted for a significant period of time.
3. Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (i.e. increased sensitivity).
4. The symptoms improve, or resolve completely, when the triggering chemicals are removed.
5. Responses occur to multiple, chemically diverse substances.
6. Symptoms include those derived from apparent CNS sensitivity, such as chemically elicited headache, fatigue, depression, anxiety, memory and concentration difficulties and confusion and cognitive dysfunction.

There are two additional issues that should be considered when deciding whether a particular patient should be allowed into a study on MCS:

- There is a huge variation in severity among different MCS patients and objective changes that may be obvious in looking at more severe MCS cases may be undiscernible when looking at more modestly affected patients. There is an argument, therefore, that one should limit admission to such studies to perhaps the most affected quarter of such patients, possibly using the Miller Quick Environmental Exposure and Sensitiviy Inventory (QEESI) questionnaire (Miller and Mitzel, 1995; Miller and Prihoda, 1999) to assess severity.
- Another issue is raised by the apparent local nature of chemical reactivity in MCS. If one is, for example, looking at responses in the lungs, one should distinguish between those patients who have asthma-type symptoms from those who do not. Similar divisions should be made for those who appear to be affected in other specific regions of the body.

XX.8 The NO/ONOO$^-$ CYCLE MECHANISM AS THE AETIOLOGICAL MECHANISM FOR MCS AND RELATED ILLNESSES

The many puzzling features of MCS are thought to require a new disease paradigm in order to explain them. This argument has been made by Bronstein (1995), Miller (1999), Rowat (1998) and Arnetz (1999). Even the MCS skeptic Gots (1996) has argued that any physiological explanation for MCS requires such a new disease paradigm. Earlier in this review, an apparently convincing argument has been made that chemicals act as toxicants in MCS, acting via different pathways, but with each producing an increase in NMDA activity. It is well established that NMDA stimulation produces increases in NO and its oxidant product ONOO$^-$ (reviewed in Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003), so that any or all of these may be involved in generating the properties of MCS.

There are many puzzling features of MCS, each of which must be explained by any proposed new paradigm. One of these is the relationship between MCS and several other related chronic illnesses, including CFS and FM and even PTSD. Several research groups have argued for a common aetiological mechanism for two, three or all four of these illnesses (Miller, 1999; Ziem and Donnay, 1995; Buchwald and Garrity, 1994; Clauw and Chrousos, 1997; Bell *et al*., 1998a; Wessely *et al*., 1999; Yunus, 2001; Pall, 2001a; Pall and Satterlee, 2001; Cohen *et al*., 2002; Buskila and Cohen, 2007). They are all comorbid with each other, they share a large number of symptoms and signs and they all share a common pattern of case initiation: cases of each are often initiated by a short-term stressor, exposure to which is followed by chronic illness. A fourth common

Table 2. The stressors implicated in the initiation of these illnesses are summarized

Illness	Stressors implicated in initiation of illness
Chronic fatigue syndrome	**Viral infection, bacterial infection, organophosphorus pesticide exposure**, carbon monoxide exposure, ciguatoxin poisoning, physical trauma, severe psychological stress, toxoplasmosis (protozoan) infection, ionizing radiation exposure
Multiple chemical sensitivity	**Volatile organic solvent exposure, organophosphorus/carbamate pesticide exposure**, organochlorine pesticide exposure, pyrethroid exposure; hydrogen sulfide; carbon monoxide; mercury
Fibromyalgia	**Physical trauma (particularly head and neck trauma), viral infection**, bacterial infection, severe psychological stress, pre-existing autoimmune disease
Post-traumatic stress disorder	**Severe psychological stress**, physical (head) trauma

The stressors indicated in bold are the ones most commonly implicated for that specific disease/illness. It should be noted that the majority of such stressors are implicated in the initiation of more than one illness. Modified from the author's web site, with permission.

feature of these illnesses is that cases of each of them are stunningly variable from one patient to another, such that we need an explanation for this variability.

So what is needed, according to this point of view, is a common aetiological mechanism which explains both the similarities and the differences among cases of these illnesses. A detailed model of these four multisystem illnesses is presented below, focussing mainly on how it plays out in MCS, but also outlining how predicted variations may explain all four of these illnesses. Then and only will the evidence be reviewed, supporting this model for MCS. Much of this discussion comes from the author's web site, with permission, and much of the evidence for it is provided in Pall (2007a) as well as other publications (Pall, 2000; Pall, 2002; Pall and Anderson, 2004).

Short-term stressors that are apparent initiators of these four illnesses are summarized in **Table 2**. You will note that each of these illnesses is initiated by multiple stressors and that these initiators include a variety of infections, physical trauma, severe psychological stress, ionizing-radiation exposure and neurotoxins such as ciguatoxin, in addition to the various chemical classes implicated in MCS initiation. These diverse stressors can all act to increase the levels of NO in the body (Pall, 2007a; Pall, 2007b; Pall, 2008; see above for MCS initiators). While each of these stressors implicated in initiation of one or more illnesses act to increase NO levels, several of these do *not* act via increased NMDA stimulation. Specifically, viral, bacterial and protozoan infections and also ionizing-radiation exposure act via induction of inducible nitric oxide synthase (iNOS) rather than acting via NMDA stimulation; NMDA receptor activation acts, in contrast, by increasing levels of intracellular calcium which stimulates, in turn, the two calcium-dependent nitric oxide synthases (NOSs), neuronal (nNOS) and endothelial (eNOS) (Pall, 2002; Moncada and Bolaños, 2006; Brown and Bal-Price, 2003). Thus it *may* be the case that MCS initiation requires increases in NMDA activity, but it is clear that CFS and FM initiation do not.

How then might short-term increases in NO produce a chronic illness? It can be argued that NO acts via its oxidant product $ONOO^-$ to initiate a complex biochemical vicious cycle that is then the cause of illness (Pall, 2007a; Pall, 2007b; Pall, 2000; Pall, 2001a; Pall, 2002), see **Figure 2**. So with each of these we have an initial cause, the short-term stressors, as well as on ongoing cause, with the ongoing cause being responsible for the properties of the chronic illness.

The vicious cycle initiated by these NO increases is shown in **Figure 2** and is centred on excessive levels of NO and its oxidant product $ONOO^-$. This vicious cycle is now being called the NO/$ONOO^-$ cycle (Pall, 2006; Pall, 2007a) (pronounced no, oh no!), based on the structures of NO and $ONOO^-$). Each of the arrows in **Figure 2** represents one or more mechanisms by which one element of the cycle acts to increase the levels of another element of the cycle. The chronic nature of these diseases is thought to be caused by the NO/$ONOO^-$ cycle, propagating itself over time through the mechanisms represented by these arrows. Most of the individual mechanisms in the cycle are based on very well-documented biochemistry (Pall, 2007a; Pall, 2000; Pall, 2002), supporting the plausibility of the cycle as a whole. Cycle elements, as shown in **Figure 2**, include not only NO and $ONOO^-$, but also superoxide, oxidative stress, the transcription factor NF-κB, the inflammatory cytokines (upper right hand corner), all three NOSs (iNOS, nNOS, eNOS), intracellular calcium levels and two types of receptors found in neuronal and non-neuronal cells, the NMDA receptor (Pall, 2007a) and the several of the TRP receptors (see above discussion; only the TRPV1 (vanilloid) receptor is shown in **Figure 2**). There are 22 distinct mechanisms that are represented by the various arrows, of which 19 are

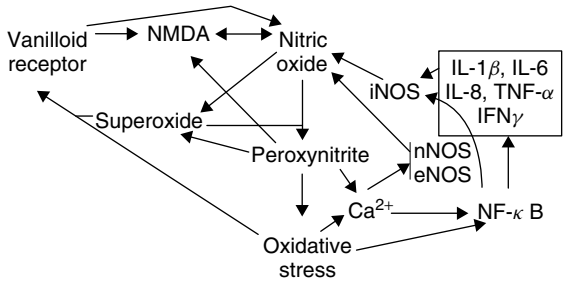

Figure 2. Vicious ($NO/ONOO^-$) cycle diagram. Each arrow represents one or more mechanisms by which the variable at the foot of the arrow can stimulate the level of the variable at the head of the arrow. It can be seen that these arrows form a series of loops that can potentially continue to stimulate each other. An example of this would be that nitric oxide can increase peroxynitrite, which can stimulate oxidative stress, which can stimulate NF-κB, which can increase the production of iNOS, which can, in turn increase nitric oxide. This loop alone constitutes a potential vicious cycle and there are a number of other loops, shown diagramatically in the figure that can collectively make up a much larger vicious cycle. The challengein these illnesses, according to this view, is to lower this whole pattern of elevations to get back into a normal range. You will note that the cycle not only includes the compounds nitric oxide, superoxide and peroxynitrite, but a series of other elements, including the transcription factor NF-κB, oxidative stress, inflammatory cytokines (in box, upper right), the three different forms of the enzymes that make nitric oxide (the nitric oxide synthases iNOS, nNOS and eNOS), and two neurological receptors, the vanilloid (TRPV1) receptor and the NMDA receptor. (The figure and legend are taken from the author's web site with permission.)

well-established, well-accepted biochemistry and physiology (Pall, 2007a; Pall, 2000; Pall, 2002; Pall and Anderson, 2004).

Of the other three, there is substantial new evidence for each of them that was not available when that section of the Pall (2007a) book was written. The impact of NO in increasing superoxide generation from the electron-transport chain in mitochondria is now increasingly accepted (Moncada and Higgs, 2006). The effect of oxidants and oxidative stress in increasing activity of TRPV1 (vanilloid receptor) and several other the TRP receptors is also now supported by much more substantial evidence (see above discussion). And Chen *et al*. (2008) have recently provided more evidence on the impact of $ONOO^-$ on the electron-transport chain in the mitochondrion, producing increased superoxide generation. Chen *et al*. (2008) also provides important new evidence on the mechanism involved in producing this increased superoxide generation. Thus all three of the previously more weakly supported mechanisms out of the 22 are now considerably more strongly supported then they were 2.5 years ago. There is a massive amount of evidence supporting the existence of the individual mechanisms proposed to make up the $NO/ONOO^-$ cycle and the only truly original aspect to it is the simple assumption that it fits together in the way that one might assume it does, based on the individual mechanisms.

Much of the mechanism outlined in **Figure 2** is classic inflammatory biochemistry—the NF-κB actions, inflammatory cytokine induction, iNOS induction, leading to increased NO, $ONOO^-$ and oxidative stress, and consequent mitochondrial dysfunction—all of these are found in every inflammatory condition. This raises the question as to whether specific chronic inflammatory diseases, and there are dozens of them, may be $NO/ONOO^-$ cycle diseases?

There are two aspects of the $NO/ONOO^-$ cycle that are not apparent from **Figure 2**. Both add further evidence for important individual mechanisms, as well as the plausibility of the overall cycle:

1. $ONOO^-$, superoxide and NO all can act via known mechanisms to lower mitochondrial function and thus adenosine triphosphate (ATP) generation (Moncada and Bolaños, 2006; Keller *et al*., 1998). $ONOO^-$ is known to attack a number of iron–sulphur proteins, including such proteins that have important roles in both the mitochondrial electron-transport chain and in the citric-acid cycle, and also leads to mitochondrial dysfunction through protein tyrosine nitration and other mechanisms (Radi *et al*., 2002; Cassina and Radi, 1996; Keller *et al*., 1998). $ONOO^-$ is also known to produce nicks in chromosomal DNA, leading in some cases to massive stimulation of poly(ADP)-ribosylation of chromosomal proteins, and because the precursor to such poly(ADP)-ribose synthesis is NAD, this can lead to massive depletion of NAD/NADH pools and consequent lowering of mitochondrial energy metabolism (Szabo, 2003; Moncada and Bolaños, 2006). Superoxide and NO also lower energy metabolism via distinct mechanisms. They both can produce lowered activity of the aconitase enzyme (Gardner *et al*., 1997; Gardner, 1997; Castro *et al*., 1994), as can $ONOO^-$. The cardiolipin in the inner membrane of the mitochondrion is very susceptible to lipid peroxidation and superoxide generated by the electron transport chain in the mitochondrion can indirectly produce major increases in such lipid peroxidation, leading to lowered activity of complexes I, III and IV and therefore lowered ATP generation (Paradies *et al*., 2001; Paradies *et al*., 2002; Musatov, 2006). NO is a competitive inhibitor of the enzyme cytochrome oxidase (complex IV) and can therefore lower the activity of the entire mitochondrial electron transport chain by lowering its terminal oxidase activity (Cassina and Radi, 1996; Galkin *et al*., 2007). The lowered ATP generation produced by this combination of mechanisms is not only important in the generation

of symptoms as a consequence of the NO/ONOO$^-$ cycle, but is also important as part of the proposed cycle itself; NMDA receptor activity is known to be activated by lowered availability of ATP, acting via two distinct mechanisms that are discussed below. Furthermore, the maintenance of low intracellular calcium levels involves much energy utilization via Ca^{+2}-ATPase and thus lowered ATP availability will tend to increase intracellular calcium levels, another predicted aspect of the NO/ONOO$^-$ cycle.

2. There are reciprocal interactions between ONOO$^-$ and a cofactor for the NOSs, tetrahydrobiopterin (BH4). ONOO$^-$ oxidizes BH4, leading to BH4 depletion and such depletion leads to what is called the partial uncoupling of all three NOSs (Pall, 2007b; Milstien and Katusic, 1999; Kohnen *et al*., 2001; Kuhn and Geddes, 2003). The uncoupled NOSs generate superoxide in place of NO. Thus, in tissues and regions of cells with high NOS activity, partial uncoupling leads to adjacent enzymes generating NO and superoxide, thus leading to almost instantaneous synthesis of ONOO$^-$. In this way, partially uncoupled NOS enzymes can act collectively as ONOO$^-$ synthases (Delgado-Esteban *et al*., 2002; Pall, 2007b). The ONOO$^-$ so generated will oxidize more BH4, thus leading to more partial uncoupling. This partial uncoupling may be central to the entire NO/ONOO$^-$ cycle leading to a shift in the ratio of NO to ONOO$^-$. That shift may be critical to the cycle in multiple ways, including generating increased activity of the transcription factor NF-κB; whereas ONOO$^-$ leads to activation of NF-κB, NO lowers NF-κB activity and thus the ratio of the two may be critical in determining the NF-κB regulatory response (Pall, 2007b).

Both of these aspects of the NO/ONOO$^-$ cycle are shown in **Figure 3**, a much more complete figure of the NO/ONOO$^-$ cycle. In it you will see the reciprocal relation between ONOO$^-$ (abbreviated PRN in the figure) and BH4 depletion. You will also see the role of ATP depletion inserted into the figure. One additional apparent aspect of the cycle is shown in the top left corner of **Figure 3**, indicated for the TRP receptors, specifically TRPV1, TRPA1 and TRPM2. TRPV1 and TRPA1 are both activated by the consequences of oxidative stress (Taylor-Clark *et al*., 2008; Bessac *et al*., 2008; Andersson *et al*., 2008; Trevisani *et al*., 2007; Puntambekar *et al*., 2005; Schultz and Ustinova, 1998; Ustinova and Schultz, 1994), as discussed above. The transfer receptor protein TRPM2, discussed above, is strongly activated by oxidants, presumably including ONOO$^-$, with such activation producing an influx of intracellular calcium which is predicted, in turn, to increase NO synthesis. The TRPM2 role in the NO/ONOO$^-$ cycle has not been proposed prior to this publication, but it may well be an important aspect of the cycle mechanism.

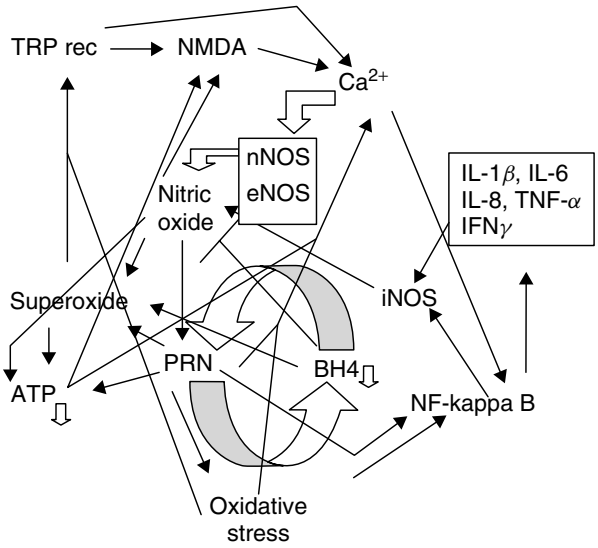

Figure 3. A more complete NO/ONOO$^-$ cycle diagram. Central to the figure are the reciprocal interactions between peroxynitrite, abbreviated as PRN and tetrahydrobiopterin (BH4) depletion. Also indicated is the ATP depletion produced by peroxynitrite, superoxide and nitric oxide. And in the upper left corner, TRP represents the three TRP receptors, TRPV1, TRPA1 and TRPM2, each of which is stimulated via distinct mechanisms by oxidative stress. Each arrow in the figure represents one or more mechanisms by which one element of the cycle stimulates another element of the cycle. (Figure and legend is taken from the author's web site with permission.)

There are three types of generic evidence that support the existence of the NO/ONOO$^-$ cycle (Pall, 2007a). By generic, I mean evidence not linked to any specific disease or illness. These are as follows:

1. Twelve studies have shown that one or both of two drugs that break down to release NO (nitroglycerine and nitroprusside) cause mammalian tissues to synthesize increased amounts of NO via all three NOSs (Chapter 1 in Pall, 2007a). These studies support the existence of a vicious cycle involving all three NOSs, as predicted by the NO/ONOO$^-$ cycle, but do not say anything about other aspects of the cycle.
2. Increased NMDA activity can increase essentially all of the NO/ONOO$^-$ cycle elements that are shown in **Figure 2** (Chapter 3 in Pall, 2007a). NMDA receptor activity directly increases intracellular calcium levels leading to increased NO levels. These studies show that most of the cycle elements can be increased simply by elevating intracellular calcium and NO, thus providing evidence for a cycle similar or identical to the NO/ONOO$^-$ cycle.
3. Hyperalgesia animal models involve all of the cycle elements shown in **Figure 2** in the generation of excessive pain in hyperalgesia (Chapter 3 in Pall,

2007a). It is difficult to explain this involvement unless the cycle ties all of these elements together.

The NO/ONOO$^-$ cycle aetiology as an explanatory model is based on five distinct principles (Pall, 2007a; Pall, 2007b; Pall, 2006; Pall and Bedient, 2007):

1. Short-term stressors that initiate cases of multisystem illnesses act by raising NO synthesis and consequent levels of NO and/or other cycle elements.
2. Initiation is converted into a chronic illness via vicious cycle mechanisms, through which chronic elevation of NO and ONOO$^-$ and other cycle elements is produced and maintained. This principle predicts that the various elements of the NO/ONOO$^-$ cycle will be elevated in the chronic phase of illness.
3. Symptoms and signs of these illnesses are generated by elevated levels of NO and/or other important consequences of the proposed mechanism, that is, elevated levels of ONOO$^-$, NO, inflammatory cytokines, oxidative stress, elevated NMDA, TRPV1 receptor activity and/or other aspects of the cycle.
4. Because the compounds involved, NO, superoxide and ONOO$^-$ have quite limited diffusion distances in biological tissues and because the mechanisms involved in the cycle act at the level of individual cells, *the fundamental mechanisms are local*.
5. Therapy should focus on down-regulating NO/ONOO$^-$ cycle biochemistry.

Of these principles, we have discussed 1 and 2 above. Principle 3 predicts that the symptoms and signs of illness can be generated by elevation of one or more elements of the cycle. Some examples of how symptoms and signs of illness may be explained by the cycle are discussed below.

Principle 4 is so important that it takes up an entire chapter (Chapter 4) in my book (Pall, 2007a). Because NO, superoxide and ONOO$^-$, the three chemical compounds most central to the NO/ONOO$^-$ cycle, have relatively short half-lives in biological tissues, they don't diffuse very far from their site of origin in the body. NO has the longest such half-life and it only diffuses about 1 mm from its origin. Furthermore, most of the mechanisms implicated by the arrows act at the cellular level. The consequence of all of this is that the NO/ONOO$^-$ cycle may be elevated in one tissue of the body, but an adjacent tissue may show little elevation and therefore be little impacted by the cycle. This local nature of the cycle biochemistry means that we can have all kinds of variations in tissue impact from one patient to another, leading in turn to all kinds of variation in symptoms and signs from one individual to another. This striking variation in symptoms from one individual to another has been repeatedly been noted in these illnesses and has been one of the great puzzles about this group of illnesses. The variation can be easily explained by the local nature of the NO/ONOO$^-$ cycle mechanism. Principle 4 does *not* suggest that there are no systemic effects, but rather that much of the cycle effects are local.

Principle 5 states that the focus of therapy should be to down-regulate NO/ONOO$^-$ cycle biochemistry. In other words, therapy should focus on lowering the cause of illness, not just on treating symptoms. This is obviously an important principle for both patients suffering from these illnesses and for conscientious physicians trying to treat them. There is much stronger evidence for principle 5 in CFS and FM (discussed below) than in the related illness MCS.

These five principles are important as a group for three distinct but overlapping reasons:

- Taken together, they produce an essentially complete explanatory model.
- The fit to each of the five produces a very different type of evidence for the causality of the cycle. Are cases of the disease/illness started by agents predicted to initiate the cycle? Are cycle elements elevated in the chronic phase of illness? Can the symptoms and signs of illness be generated by one or more the elements of the cycle? Is there evidence for a local mechanism? Can the disease/illness be treated by agents predicted to down-regulate the cycle?
- Because the fit to each of the five gives a very different type of evidence for causality of the cycle, the fit to each of them provides a distinct criterion as to whether a particular disease/illness is a good candidate for being a NO/ONOO$^-$ cycle disease.

What the author has done, in his book and elsewhere, then, is to use these five criteria to ask whether each multisystem illness and also a number of other diseases are good candidates for inclusion under the NO/ONOO$^-$ cycle mechanism. It is the goal, then in a following section of this chapter to go through each of the criteria to see how good the fit is for MCS.

In summary, there are three distinct types of evidence that support the general notion that the NO/ONOO$^-$ cycle mechanism in an important paradigm of human disease.

1. The individual mechanisms of the cycle, represented by the arrows in **Figures 2** and **3**, are almost all well-documented biochemistry and physiology.
2. There are three generic types of evidence for the existence of the cycle, that is evidence not linked to any specific disease or illness.
3. There are a number of diseases/illnesses where one can argue based on the fit to the five principles outlined above, that they are good candidates for inclusion under the NO/ONOO$^-$ cycle paradigm.

XX.8.1 NO/ONOO⁻ Cycle Mechanisms for the Generation of Shared Symptoms and Signs of Illness

It has been widely claimed that these multisystem illnesses and even their symptoms are unexplained. Clearly, for the NO/ONOO⁻ cycle mechanism to be plausible for these multisystem illnesses, it must be possible to explain the symptoms and signs of illness as being generated by one or more elements of the cycle. Such explanations are needed for both the specific symptoms and signs and the shared ones, discussed here (**Table 3**). In Chapter 3 of Pall (2007a), evidence is provided on how these shared symptoms and signs may be generated by the NO/ONOO⁻ cycle aetiology. The mechanisms listed in **Table 3** are *not presented as established mechanisms in these illnesses*, but they are plausible mechanisms based on substantial scientific information. Each of these only occurs in some multisystem illness sufferers, consistent with the striking variation of symptoms and signs that are a characteristic feature of these illnesses. Indeed it may be argued that the defining symptoms and signs of CFS, MCS, FM and PTSD are found in all sufferers of each of these illnesses because we required them for the diagnosis. In other words, we appear to have a very large spectrum of illness that we have more or less arbitrarily subdivided via particular symptoms.

XX.9 FUSION OF THE NO/ONOO⁻ CYCLE MECHANISM WITH NEURAL SENSITIZATION AND OTHER PUTATIVE MCS MECHANISMS

While what has become the NO/ONOO⁻ cycle has produced fairly complete explanations of such illnesses as CFS and FM and also of a number of additional, well-established diseases (Pall, 2007a; Pall and Bedient, 2007), it alone did not produce a compelling explanation for the complexities of MCS (Pall and Satterlee, 2001). It was only when fused with a previous MCS model, the neural sensitization model, that a much more complete explanation became apparent.

Bell and her collaborators (Bell *et al*., 1992; Bell *et al*., 1999a; Bell *et al*., 2001a) and others (Antelman, 1994; Rossi, 1996; Friedman, 1994; Sorg and Prasad, 1997) proposed a neural sensitization model, where chemicals were proposed to act to greatly increase neural sensitization in the brain, particularly in the limbic system. The notion here is that if chemicals can act to produce such neural sensitization, greatly increasing the activity of synapses over large regions of the brain, that this could explain the basic mechanism of MCS. In this way, chemicals might generate changes in EEG activity (Lorig *et al*., 1991; Bell *et al*., 1999b; Bell *et al*., 2001b; Fernandez *et al*., 1999; Muttray *et al*., 1995) and also in brain PET scans (Heuser and Wu, 2001; Hillert *et al*., 2007) and SPECT scans (Simon *et al*., 1994; Heuser *et al*., 1994; Fincher *et al*., 1997a; Fincher *et al*., 1997b) in MCS. There was a New York Academy of Sciences meeting in 2000 that focussed on the proposed neural sensitization mechanism for MCS (Sorg and Bell, 2001) and there is no question that at that time, this neural sensitization view was the most influential view of a possible physiological basis for MCS. Ashford and Miller (1998) listed 10 compelling similarities between MCS and neural sensitization, each of which may be considered to be evidence in favour of a neural sensitization model.

Nevertheless, the neural sensitization interpretation of MCS never generated explanations of how the various classes of chemicals may work nor how the roughly 1000-fold increase in chemical sensitivity that appears to occur in many MCS patients might be generated, nor the similarities to CFS and related illnesses. It did provide a framework for explaining the chronic nature of chemical sensitivity, namely long-term changes in synaptic sensitivity.

The most important mechanism of such neural sensitization is that of LTP, the main mechanism involved in learning and memory. The LTP mechanism is involved on a highly selective basis in strengthening synaptic interactions in the process of learning and memory, and the question raised by its possible role in MCS is what will be the consequences if chemical exposure leads to a massive activation of this process?

In the process of neural sensitization, changes in each synapse involve changes in both the presynaptic and the postsynaptic neurons. LTP is known to involve, as key elements in a complex overall mechanism activated in the postsynaptic neuron, several elements of the NO/ONOO⁻ cycle, notably NMDA activity, NO and intracellular calcium (Albensi, 2001; Bliss and Collingridge, 1993; Bennett, 2000; Platenik *et al*., 2000; Dineley *et al*., 2001; Prast and Phillippu, 2001; Cotman *et al*., 1988). Superoxide, another cycle element also has a role, albeit a complex one (Knapp and Klann, 2002; Hu *et al*., 2007). Increased NMDA activity in the postsynaptic neuron has a role, as do the increases in intracellular calcium and NO produced by such NMDA stimulation of the postsynaptic neuron (Albensi, 2001; Bliss and Collingridge, 1993; Bennett, 2000; Platenik *et al*., 2000; Dineley *et al*., 2001; Prast and Phillippu, 2001; Cotman *et al*., 1988). NO produced in the postsynaptic neuron, acts as what is called a retrograde messenger, diffusing back to the presynaptic neuron and causing it to be more active in neurotransmitter release, including the release of glutamate, the major physiological agonist of the NMDA receptors (Zhang and Snyder, 1995; Kuriyama and Ohkuma,

Table 3. Explanations for symptoms and signs

Symptom/sign	Explanation based on elevated nitric oxide/peroxynitrite theory
Energy metabolism/mitochondrial dysfunction	Inactivation of several proteins in the mitochondrion by peroxynitrite; inhibition of some mitochondrial enzymes by nitric oxide and superoxide; NAD/NADH depletion; cardiolipin oxidation
Oxidative stress	Peroxynitrite, superoxide and other oxidants
PET scan changes	Energy metabolism dysfunction leading to change transport of probe; changes in perfusion by nitric oxide, peroxynitrite and isoprostanes; increased neuronal activity in short-term response to chemical exposure
SPECT scan changes	Depletion of reduced glutathione by oxidative stress; perfusion changes as under PET scan changes
Low NK (natural killer) cell function	Superoxide and other oxidants acting to lower NK cell function
Other immune dysfunction	Sensitivity to oxidative stress; chronic inflammatory cytokine elevation
Elevated cytokines	NF-κB stimulating of the activity of inflammatory cytokine genes
Anxiety	Excessive NMDA activity in the amygdala
Depression	Elevated nitric oxide leading to depression; cytokines and NMDA increases acting in part or in whole via nitric oxide.
Rage	Excessive NMDA activity in the periaqueductal grey region of the mid-brain
Cognitive/learning and memory dysfunction	Lowered energy metabolism in the brain, which is very susceptible to such changes; excessive NMDA activity and nitric oxide levels and their effects of learning and memory
Multiorgan pain	All components of cycle have a role, acting in part through nitric oxide and cyclic guanosine monophosphate (cGMP) elevation
Fatigue	Energy metabolism dysfunction
Sleep disturbance	Sleep impacted by inflammatory cytokines, NF-κB activity and nitric oxide
Orthostatic intolerance	Two mechanisms: nitric oxide-mediated vasodilation leading to blood pooling in the lower body; nitric oxide-mediated sympathetic nervous system dysfunction
Irritable bowel syndrome	Sensitivity and other changes produced by excessive vanilloid and NMDA activity, increased nitric oxide
Intestinal permeabilization leading to food allergies	Permeabilization produced by excessive nitric oxide, inflammatory cytokines, NF-κB activity and peroxynitrite; peroxynitrite acts in part by stimulating poly(ADP)-ribose polymerase activity

Taken from the author's web site with permission. It should be noted that while each of these are plausible mechanisms and, in most cases well-documented mechanisms under some pathophysiological circumstances, in most cases their role in generating these symptoms in these multisystem illnesses is *not* established. The role of reduced glutathione depletion in generating SPECT scan changes is documented in Jacquier-Sarlin *et al*., 1996 and in Suess *et al*., 1991.

1995; Williams, 1996). LTP involves not only increased glutamate release, but also changes in the postsynaptic neuron, making its synapses more sensitive to stimulation.

One point that needs to be made is that we have a striking convergence between the demonstrated role of each of the chemicals implicated in MCS, producing increased NMDA activity, and the essential role of NMDA receptors in LTP. This convergence provides, therefore, for the first time, an explanation for that pattern: only chemicals leading to increased NMDA activity may be expected to produce an up-regulation of the LTP mechanism.

Whereas the normal, highly selective role of LTP in learning and memory will not be expected to involve any substantial NO/ONOO$^-$ cycle elevation, a massive stimulation of NMDA activity over substantial regions of the brain, produced by chemical exposure, will be expected to involve substantial NO/ONOO$^-$ cycle elevation. The extraordinary chemical sensitivity seen in MCS, at least in the CNS-related symptoms, may then be generated by the following multiple mechanisms:

1. Subsequent chemical exposure will stimulate regions of the brain with already existing neural sensitization, with that neural sensitization maintained both by the standard LTP mechanism *and* by the local elevation of the NO/ONOO$^-$ cycle. This combination may be exacerbated by a series of mechanisms, each involving elements of the NO/ONOO$^-$ cycle, as follows.
2. NO acting as a retrograde messenger will act to stimulate further glutamate release by the presynaptic neurons.

3. Energy metabolism dysfunction produced by $ONOO^-$, superoxide and NO will cause NMDA receptors to be hypersensitive to stimulation. It is known that energy-metabolism dysfunction produces a decreased membrane potential which acts, in turn, to cause the NMDA receptors in such cells to be hypersensitive to stimulation (reviewed in Novelli *et al*., 1988; Schulz *et al*., 1997; Turski and Turski, 1993; Pall, 2002).
4. Energy-metabolism dysfunction also acts on glial cells which normally rapidly lower extracellular glutamate via energy-dependent glutamate transport. Lowered energy metabolism will then lead to increased extracellular glutamate, leading in turn to increased NMDA stimulation (Gadea and Lopez-Colome, 2001; Bliss *et al*., 2004).
5. $ONOO^-$ leads to a partial breakdown of the blood–brain barrier, leading to increased chemical access to the brain (reviewed in Phares *et al*., 2007; Pall, 2002; Pall, 2003). Kuklinski *et al*. (2003) have reported blood–brain barrier breakdown in MCS patients and there is also an animal model of MCS in which similar breakdown has been observed (Abdel-Rahman *et al*., 2002; Abu-Qare and Abou-Donia, 2003; Abou-Donia *et al*., 2002b).
6. Many of the chemicals implicated in MCS are metabolized via cytochrome P450 activities and these enzymes are known to be inhibited by NO, thus possibly leading to increased accumulation of the active chemical forms (reviewed in Pall, 2002).
7. Finally TRPV1, TRPA1 and some other TRP receptors are activated through the action of oxidants, as discussed above, and organic solvents and other agents that act via these TRP receptors, such as some mould toxins, may be expected to have increased activity due to such TRP receptor activation.

This combination of multiple mechanisms, each multiplying the actions of the others, is predicted to easily produce the roughly 1000-fold increase in sensitivity that appears to occur in many MCS patients. So we have, for the first time, a hypothesis that explains the last major puzzle in MCS, how one can get this stunning increase in apparent sensitivity to such wide variety of chemicals. Having said that, while each of these mechanisms are individually well-documented and we do have aspects of some of them reported to occur in MCS, there is no currently available evidence that directly and convincingly implicates any of them in producing MCS-related sensitivity. This is not surprising, given the extraordinarily low level of research support that has been available for MCS studies.

XX.10 PERIPHERAL SENSITIVITY MECHANISMS

MCS patients typically not only have central sensitivity symptoms that can be attributed to neural sensitization/NO/$ONOO^-$ cycle mechanisms, but also peripheral sensitivities. They often have chemical sensitivity in the upper respiratory tract, leading to rhinitis symptoms on low-level chemical exposure, they have asthma-type symptoms in response to low-level chemical exposures, they have skin sensitivities, with different patterns of skin involved in different patients, they have gastrointestinal (GI) tract sensitivities and additional organ sensitivity may be seen (Ashford and Miller, 1998). These are likely to be local sensitivity mechanisms distinct from the CNS-derived sensitivity discussed in the preceding section.

Meggs (1994; 1997), Meggs *et al*. (1996) and Bascom *et al*. (1997) and others have described the initiation of cases of RADS, where a type of asthma is initiated by chemical exposure to organic solvents and other irritants and the pattern of chemicals involved is similar or identical to those involved in MCS initiation. RADS is characterized by a wide-ranging chemical sensitivity (Meggs, (1994; 1997); Meggs *et al*., 1996; Bascom *et al*., 1997; Krishna *et al*., 1998), in addition to the more commonly studied sensitivities of asthma, those to allergens, exercise and cold. Not only are organic solvents involved, but several classes of pesticides as well (Proudfoot, 2005; Hernández *et al*., 2008; Proskocil *et al*., 2008; Fryer *et al*., 2004). Sensitization of the bronchi in response to chemical exposure, including organic solvent and pesticide exposure and also other irritants may well be commonly involved in causing occupational asthma (Jeebhay and Quirce, 2007; Gautrin *et al*., 1994). Interestingly, cases of asthma can also be apparently initiated, not only by organic solvents or pesticide chemicals, but also by exposure to mould toxins in mould-infested 'sick buildings', another similarity with MCS (Sahakian *et al*., 2008; Lee, 2003; Mahmoudi and Gershwin, 2000). Thus reactive airways disease can be seen as a common aspect of MCS, with a strikingly similar pattern of chemicals involved in the initiation process.

In addition to RADS, there is also reactive upper airways dysfunction syndrome (RUDS), in which there is chemical sensitivity initiated by previous chemical exposure, producing inflammatory responses in the upper airways, leading to rhinitis symptoms as well as ultrastructural changes (Meggs, 1994; Meggs, 1997; Meggs *et al*., 1996). Similar to RADS and RUDS, there is also a reactive intestinal dysfunction syndrome (RIDS), where chemical exposure can initiate intestinal chemical sensitivity (Lieberman and Craven, 1998).

Peripheral sensitivity in the skin, lungs, upper respiratory tract, GI tract and other tissues, raises the question

of how the mechanism of sensitivity may differ from that found in the central sensitivity discussed above? It seems likely, given the similar spectrum of chemicals involved at least in the RADS/airways response, that it also involves an NMDA stimulation pathway. There is evidence for an excessive NMDA role in asthma (Hirota and Lambert, 1996; Overstreet and Djuric, 1999; Dickman *et al*., 2004; Hoang *et al*., 2006; Said *et al*., 2001) and also for an NMDA role in skin-sensitivity responses produced by formaldehyde (Elliott *et al*., 1995; Coderre and Melzack, 1992). In MCS patients, the NMDA antagonist dextromethorphan seems to lower sensitivity responses, not only associated with central sensitivity, but also associated with peripheral sensitivity (Dudley, 1998). Glutamate ingestion of MCS patients appears to trigger symptoms associated with peripheral sensitivities, not just central (Miller and Prihoda, 1999; Ross, 1997). All of these observations suggest an NMDA mechanism in peripheral sensitivity, although the strength of the evidence on this is relatively weak. However, it seems reasonable, given the broad range of chemicals involved in these peripheral sensitivity responses, and the known action of these chemicals as producing NMDA stimulation, that NMDA receptor stimulation may well be involved in peripheral sensitivity, as it is in central sensitivity.

So what mechanisms may be likely to be involved in generating peripheral sensitivity? Clearly, of the seven mechanisms postulated for central sensitivity, one, the breakdown of the blood–brain barrier cannot be involved, and a second, the role of NO acting as a retrograde messenger is unlikely to be involved. The other five, however, may well have a role. And additional mechanisms may also be involved. Meggs has published biopsy studies of chemically sensitive peripheral tissues suggesting that neurogenic inflammation has an important role in generating the sensitivity of these peripheral tissues (Meggs, 1993; Meggs, 1997; Bascom *et al*., 1997). Neurogenic inflammation may be expected to be generated by elements of the NO/ONOO$^-$ cycle, including TRPV1 activity, NF-κB activity and NO (Leffler *et al*., 2008; Kajekar *et al*., 1995; Yonehara and Yoshimura, 1999; Ruocco *et al*., 2001; Pall and Anderson, 2004; Lieb *et al*., 1997; Lin *et al*., 2007) and because of its inflammatory action, will be expected, in turn to stimulate the cycle. Mast cell activation, an aspect of neurogenic inflammation (Ruocco *et al*., 2001; Hu *et al*., 2008; Costa *et al*., 2008), has been reported to be involved in MCS (Heuser, 2000; Heuser, 2001), and observations providing further support for mast-cell activation in MCS have been provided by Kimata (2004) and Elberling *et al*. (2007). Such mast-cell activation by chemical exposure may also be expected to act to exacerbate the cycle, through inflammatory cytokine elevation and other mechanisms. Mast-cell activation is reported to be stimulated by TRPV1 activation and also by NF-κB (Hu *et al*., 2008; Kempuraj *et al*., 2003; Lee *et al*., 2007), both NO/ONOO$^-$ cycle elements.

In summary, we have a number of locally acting mechanisms that are expected to act synergistically with each other to produce high levels of peripheral chemical sensitivity:

1. Chemical stimulation of regions of the body with elevated NO/ONOO$^-$ cycle activities.
2. Lowered mitochondrial function leading to increased NMDA receptor activity.
3. Lowered mitochondrial function leading to lowered local glutamate transport and therefore to increased NMDA stimulation.
4. NO inhibition of local cytochrome P450 activity and thus lowered metabolism of chemicals implicated in chemical sensitivity.
5. Local oxidative stress and ONOO$^-$ elevation, leading to increased activity of TRPV1, TRPA1, TRPM2 and possibly other TRP receptor activities, leading to both increased chemical sensitivity via these receptors and amplification of the inflammatory response by TRPM2.
6. Neurogenic inflammation produced, in part, by TRPV1 stimulation and NO, leading in turn to increased inflammation.
7. Mast-cell activation, generated in part by TRPV1 stimulation and NF-κB activity, leading in turn to increased inflammation.

It should be emphasized that while these individual mechanisms are well documented, their causal role in producing local peripheral chemical sensitivity in MCS is undocumented for most mechanisms and needs further substantial study in the others. At this point, they should be viewed as plausible predictions of the NO/ONOO$^-$ cycle fusion model which produce, in turn, plausible explanations of the peripheral sensitivities found in MCS.

XX.11 THE NO/ONOO$^-$ CYCLE MECHANISM AS EXPLAINING PREVIOUSLY UNEXPLAINED MCS PROPERTIES

The title of the author's book *Explaining 'Unexplained Illnesses'* (Pall, 2007a) is obviously a challenge to those who have repeatedly claimed that this whole group of multisystem illnesses is unexplained, and there is no doubt that MCS has been the most challenging of this group of illnesses to explain. Kuhn, in his famous book *The Structure of Scientific Revolutions* makes clear that new scientific paradigms, developed from what he calls 'revolutionary science' (as opposed to 'normal

science'), are judged in large measure by how well they explain previously unexplained properties of the scientific phenomena to which the paradigm may be expected to apply. That is, one does not only look at the available data and how well it supports the proposed new paradigm, but one needs to look carefully at how well it explains the many relevant, but previously unexplained properties.

Given the previous challenges in explaining MCS, one needs to ask how well the NO/ONOO$^-$ cycle fusion model for MCS explains its many previously puzzling properties. I will go through 12 of these one at a time, using a question-and-answer format. Citations are provided to document issues that were not documented above.

1. How can so many diverse chemicals produce a common response, namely initiating cases of MCS and also eliciting responses in those already chemically sensitive? By acting along different pathways to produce a series of common responses, notably increased NMDA activity, intracellular calcium, NO and ONOO$^-$.
2. Why is MCS chronic? Because the NO/ONOO$^-$ cycle propagates itself over time and probably, in addition, because of long-term changes in the synapses of the brain, leading to neural sensitization.
3. How can MCS patients be so exquisitely sensitive to low-level chemical exposure, with many estimated to be on the order to 1000 times more sensitive than normal? Possibly by a series of mechanisms in the brain predicted to lead to long-term changed neural sensitization, increased short-term sensitization, increased levels of neurotransmitter (glutamate) and increased chemical accumulation. Peripheral sensitivity may involve some of these mechanisms as well and also such mechanisms as neurogenic inflammation and mast cell activation. Two of the transient receptor potential receptors may also have roles in amplifying sensitivity responses. It is through a combination of such mechanisms, acting synergistically with each other, that such high-level sensitivity may be produced.
4. Why is MCS comorbid with such diseases/illness as CFS, FM, PTSD, tinnitus and asthma? Possibly because each of these may be NO/ONOO$^-$-cycle mechanisms and each of them certainly involves elements of the NO/ONOO$^-$ cycle in their aetiology.
5. How can diverse organic solvents be involved in MCS? Probably by stimulating, either directly or through their metabolic products, several of the TRP receptors including the TRPV1 and TRPA1 receptors. This same group of receptors is involved in the SI response to a similar or identical set of organic solvents.
6. Why are symptoms so variable from one patient to another? Because the NO/ONOO$^-$ cycle is fundamentally local, such that one can have both quantitative and qualitative variable tissue impact in different patients. This same mechanism leads to similar variability in cases of CFS, FM and PTSD.
7. Several research groups have reported apparent lowered activity of the porphyrin biosynthetic pathway, leading to accumulation of compounds derived from intermediates at multiple steps in this pathway (Downey, 2001; Matthews, 1998; Morton, 1997; see also Hahn and Bonkovsky, 1997). How can such multiple steps in the pathway be lowered? Probably because of the role of NO in regulating this pathway (Kim *et al*., 1995; Rafferty *et al*., 1996) and possibly because the last step in the pathway is an iron–sulphur protein (Dailey *et al*., 2000) and such iron–sulphur proteins are often inactivated by ONOO$^-$ or NO (Soum *et al*., 2003).
8. How can neurogenic inflammation be involved in MCS? Probably because NO/ONOO$^-$-cycle elements, including TRPV1 receptor activity and NO, can stimulate neurogenic inflammation.
9. How can mast-cell activation be involved in MCS (Pall, 2003)? Probably because both TRPV1 receptor activity and NF-κB can stimulate mast cells.
10. It has been shown that repeated or continuous low-level exposure to organic solvents can lead to desensitization/masking of the MCS response (Ashford and Miller, 1998). What mechanism is involved here? Probably by the lowering of TRPV1 and other TRP receptor activity in response to such exposure to many TRPV1 agonists (Reviewed in Pall and Anderson, 2004; Szallasi, 2002). Interestingly, the TRPA1 receptor, also suggested above to be involved in responding to organic solvents in MCS, is also reported to be down-regulated under these conditions (Akopian *et al*., 2007), consistent with a role for these receptors in masking/desensitization. The desensitization to very small amounts of xenobiotics applied as part of a therapeutic programme (Weaver, 1996; Rea, 1997) may also be produced by this same process.
11. How can moulds in 'sick-building situations' initiate cases of MCS? Probably because mycotoxins produce inflammatory responses and some mycotoxins can stimulate the TRPV1 receptor.
12. How should MCS be treated? Through chemical avoidance and the use of agents that lower aspects of the NO/ONOO$^-$ cycle, including antioxidants, agents that lower NO, ONOO$^-$ and superoxide production, agents that improve mitochondrial function, agents that lower inflammatory biochemistry, agents that lower excitotoxicity, including excessive NMDA activity and agents that help restore BH4.

It can be seen from the above that there are reasonable explanations derived from the NO/ONOO$^-$ cycle mechanism, as it applies to MCS, for each of these puzzling questions. Previously, as best I can determine, only one of these had a good explanation: the chronic nature of MCS could be explained by the long-term synaptic changes produced by neural sensitization, but, even here, this is probably only part of the explanation and additional NO/ONOO$^-$ cycle mechanisms may be likely to be involved.

XX.12 ANIMAL MODEL DATA ON VARIOUS ASPECTS OF THE PROPOSED NO/ONOO$^-$-CYCLE MECHANISM OF MCS

A whole series of animal models suggested as models for MCS have provided evidence for roles of various aspects of the NO/ONOO$^-$ cycle fusion model as it is proposed to apply to MCS. These include the following.

Sorg *et al*. (1998; 2001) developed a rat model showing cross-sensitization to cocaine and formaldehyde. Cocaine is known to also produce increases in NMDA activity (Laso, 2001; McGinty, 1995), as do the various initiators of cases of MCS. Her studies provide evidence for both neural sensitization and cross-sensitization. von Euler *et al*. (1994) described a similar rat model, using primarily toluene instead of formaldehyde as their main sensitizing agent, that appears to provide evidence for both neural sensitization and cross-sensitization.

Cocaine was also used in a mouse sensitization model which produced convincing evidence for cross-sensitization and increased NMDA activity, as well as an essential role of increased NO in producing the neural sensitization (Balda *et al*., 2008; Itzhak and Martin, (1999; 2000); Itzhak *et al*., 1998; Itzhak, 1995).

Gilbert (2001) reviewed an animal kindling model in response to repeated or high-level exposure to lindane and other similar pesticides, in which neural sensitization leads to overt seizure activity. The mechanism is essentially identical to the mechanism outlined earlier in this paper where pesticide produces decreased $GABA_A$ function, leading in turn to increased NMDA activity, increased subsequent intracellular calcium levels, acting in turn to produce LTP and consequent neural sensitization, leading in this situation to overt seizure activity. Cloutier *et al*. (2006) has also discussed the role of lindane in initiating an animal model for MCS and Adamec (1994) has discussed a different $GABA_A$ antagonist as such an initiator.

The mouse model of Anderson and Anderson (1999a, 1999b, 2003) of all MCS animal models is the one that has been shown to be at least superficially most similar to MCS in humans. It involves sensitization to a number of chemical mixtures implicated in MCS, cross-sensitization among different chemicals and chemical mixtures and also linkage to the SI response.

Willis (2001) described a primate model of central sensitization leading to secondary hyperalgesia and allodynia following repeated injections of capsaicin, the classic TRPV1 agonist. It provides evidence for, not only TRPV1 involvement, but also for NMDA, NO and intracellular calcium involvement, in addition, of course, to neural sensitization. Thus we have evidence of roles for five of the important elements of the model. Similar responses were reported earlier from formaldehyde injections.

Abou-Donia and his colleagues have published the most extensive studies on an animal (rat) model of MCS (Abou-Donia, 2002b). The toxicants they studied were all toxicants that the 1991 Gulf War veterans were exposed to and are therefore potentially involved in the initiation of Gulf War syndrome or illness. The Gulf War syndrome veterans suffer from MCS or an MCS-like illness (Proctor *et al*., 2001; Reid *et al*., 2001; Miller and Prihoda, 1999; Thomas *et al*., 2006), along with symptoms of other multisystem illnesses, CFS, FM and PTSD (Chapter 10, Pall, 2007a). Consequently, this rat model may be considered to be a model both for MCS and for the related Gulf War syndrome.

The specific chemicals studied by Abou-Donia and his colleagues, both individually and in combination, included the carbamate acetylcholinesterase inhibitor, pyridostigmine bromide, the insect repellant and irritant DEET (*N,N*-diethyl-*m*-toluamide) (Schoenig *et al*., 1993; Robbins and Cherniack, 1986), the pyrethroid pesticide, permethrin, depleted uranium and several organophosphorus toxicants. Of these only the depleted uranium is apparently not related to initiators of cases of MCS. In these studies, exposure to these toxicants has been found to produce chronic neurological changes, including neurobehavioural changes and sensorimotor deficits, from high-level exposures or from long-term, subclinical exposures (Abou-Donia, 2003; Abou-Donia *et al*., 2001; Abou-Donia *et al*., 2002a; Abou-Donia *et al*., 2002b; Abou-Donia *et al*., 2004; Abdel-Rahman *et al*., 2004a; Abdel-Rahman *et al*., 2004b). Even doses that show no signs of overt neurotoxicity produce these real, measurable and chronic neurological changes (Abdel-Rahman *et al*., 2004b).

Among the important physiological changes following chemical exposure are elevation of 3-nitrotyrosine levels, a marker of ONOO$^-$ elevation, oxidative stress as measured by elevation of 8-hydroxy-2′-deoxyguanosine levels, disruption of the blood–brain barrier and elevated NO levels (Abou-Donia *et al*., 2002b; Abu-Qare and Abou-Donia, 2001a; Abu-Qare and Abou-Donia, 2001b; Abu-Qare and Abou-Donia, 2003; Abu-Qare *et al*., 2001; Abdel-Rahman *et al*., 2002), all predicted consequences of the NO/ONOO$^-$ cycle mechanism.

Abou-Donia and coworkers reported synergistic interactions of these chemicals (Abou-Donia *et al*., 1996; Abu-Qare and Abou-Donia, 2001a; Abu-Qare and Abou-Donia, 2003; Abdel-Rahman *et al*., 2002) and others have found such synergistic effects in animal models as well (reviewed in Research Advisory Committee on Gulf War Veterans Illnesses., 2004). They suggest at least three mechanisms for the synergistic chemical interactions: competition for a cytochrome P450 degradative enzyme (Abu-Qare and Abou-Donia, 2008); partial breakdown of the blood–brain barrier produced by one chemical, leading to increased brain sensitivity to a second chemical (Abou-Qare and Abou-Donia, 2003) and competition for cellular excretion via P-glycoprotein (El-Masry and Abou-Donia, 2006). The author suggests additional possible mechanisms for such synergism, including the synergistic action of different organic solvents, acting as TRPV1 agonists and chemical action along multiple pathways, each leading to increased NMDA activity. The synergistic interactions among chemicals produce great difficulties for toxicologists attempting to estimate the toxicity of complex mixtures of chemicals from the toxicity of the individual components.

Two chemicals and one mixture of chemicals, all implicated in cases of MCS were studied in a mouse model by Fujimaki and colleagues. They demonstrated increases in inflammatory cytokines and reactive airways disease inflammation, as well as changes in CNS neurological activity (Tin-Tin-Win-Shwe *et al*., 2007; Fujimaki *et al*., 2001; Fujimaki *et al*., 2004; Fujimaki *et al*., 2007). A causal role of the cytokine IL-6 in the generation of lung inflammation in response to diesel exhaust was demonstrated by comparing an IL-6 gene knockout mouse with the wild-type (Fujimaki *et al*., 2006).

Low-level exposure of several noxious chemicals, including formaldehyde, to mouse skin generated progressive sensitization, leading to both neurogenic inflammation and increased inflammatory cytokine levels (Nakano, 2007).

Fukuyama *et al*. (2008) reported on an MCS mouse model, in which repeated applications of three chemical sensitizers were used to produce sensitivity, followed by a challenge with the same sensitizer. They found that the levels of several inflammatory cytokines were elevated following sensitization and that the challenge produced a much larger cytokine elevation. Thus the pattern of exposure and the response closely parallel the pattern of chemical exposure and subsequent elicitation of sensitivity responses seen in MCS. One of the sensitizers used, TDI is known to be a TRPV1 agonist.

Plitnick *et al*. (2002) showed that the chemical sensitizers, trimellitic anhydride and dinitrochlorobenzene, known to produce airway chemical sensitivity or skin chemical sensitivity, produced increases in some inflammatory cytokines in a mouse model. Harry *et al*. (2002) also showed sensitizer induction of inflammatory cytokine mRNA in glial cells in culture.

It can be seen from the above, that a surprising number of NO/ONOO$^-$ cycle MCS fusion model elements have been found to be involved in MCS animal models. These include both neural sensitization and cross-sensitization between chemicals, as well as progressive sensitization; chemical agents that are known to act by decreasing acetylcholinesterase or $GABA_A$ activity or increasing TRPV1 or sodium channel activity; chemical linkage to the SI response; increases in NMDA activity, NO, ONOO$^-$, oxidative stress, inflammatory cytokines, intracellular calcium, neurogenic inflammation, airways sensitivity and inflammation; and breakdown of the blood–brain barrier. Most, but not all, of these have been shown to have substantial causal roles in the generation of the animal model response. Although we have evidence from these animal models for roles of many features of the NO/ONOO$^-$ cycle mechanism, as it is proposed to apply to MCS, generally, two to five of these aspects have been looked at in each animal model and it is unclear whether any single animal model will involve all of these. However, given the fact that none of these studies have been done to test the NO/ONOO$^-$ cycle mechanism, and funding for such studies has been very limited, there is a surprising amount of data supporting aspects of the cycle mechanism.

XX.13 POSSIBLE SPECIFIC BIOMARKER TESTS? OBJECTIVELY MEASURABLE RESPONSES TO LOW-LEVEL CHEMICAL EXPOSURE

One of the obvious needs in this area of medical research, is the need for one or more specific biomarker tests that can be used to objectively confirm a diagnosis of MCS. There are similar needs for such tests for CFS and FM as well. Because the aetiological mechanism of each of these is thought to be centred on the NO/ONOO$^-$ cycle and the cycle is mostly inflammatory biochemistry, looking at whole-body markers of the consequences of such inflammatory biochemistry will not be useful as a specific biomarker test. There are many dozens of inflammatory diseases, including many chronic inflammatory diseases, so prolonged elevation of such markers will be nonspecific. Furthermore, because such chronic inflammatory diseases are so common, in most cases such markers for MCS patients will often be in the normal range, because typically abnormally elevated levels are usually defined as being two standard deviations above the norm. It is only when one compares sizable groups of MCS patients with controls that one is likely to see statistically significant differences. All of these issues create difficult challenges in trying to develop specific biomarker tests.

Given these challenges, it may be predicted that specific biomarker tests for any NO/ONOO$^-$ cycle illness must directly or indirectly measure the impact of the cycle on whatever tissue or tissues must be involved in that specific illness. In most cases of MCS, there may be many such tissues, and the obvious way to look at the impact of the cycle on those tissues is to look at the chemical sensitivity responses in one of these tissues. We need to compare the responses of MCS patients with those of controls to low-level chemical exposure, looking at one or more objectively measurable responses. The NO/ONOO$^-$-cycle mechanism predicts that such low-level chemical exposure will produce elevated responses of NO/ONOO$^-$ cycle elements in MCS patients, but little response in normal controls. Alternatively, one might look at the consequences of NO/ONOO$^-$-cycle elevation produced by low-level chemical exposure, rather than specific cycle elements themselves. There have been quite a number of studies reporting elevated responses to low-level chemical exposure in MCS patients, as compared with controls, and this section of the chapter summarizes some of these and compares those reported responses with those predicted from the NO/ONOO$^-$-cycle mechanism of MCS. Studies of neuropsychological changes following low-level chemical exposure will not be reviewed here because the author has no competence to judge such studies.

The most extensive studies of this type are the cough responses studied by Millqvist and her colleagues in response to capsaicin challenge (Johansson *et al*., 2002; 2006; Millqvist, 2000; Ternesten-Hasséus *et al*., 2002; Millqvist *et al*., 2005; Millqvist *et al*., 2008). In these repeated studies, MCS patients show much elevated cough responses over normal controls in response to low-level capsaicin challenge. Capsaicin is the classic TRPV1 agonist and because TRPV1 receptor activity is thought, as argued above, to be involved in the responses to many organic solvents and related chemicals, this response appears to be quite consistent with what may be predicted by the NO/ONOO$^-$ cycle mechanism, as it is proposed to play out in MCS. Because the cough response produced by capsaicin is lowered by the use of dextromethorphan and other NMDA antagonists (Kamei *et al*., 1989; Capon *et al*., 1996; Chung, 2005), this pathway of action appears to be identical to that proposed for TRPV1 action in MCS. Millqvist *et al*. (2005) also report substantial increases in nerve growth factor (NG) activity following low-level capsaicin provocation in MCS patients, but not in controls, as predicted by two aspects of the NO/ONOO$^-$ cycle, up-regulation of TRPV1 activity and neurogenic inflammation. These responses are almost certainly local ones, as suggested by Millqvist (2000), so that the minority of MCS sufferers who do not have respiratory tract sensitivity, will not be expected to have such elevated cough responses to such capsaicin provocations.

Hillert *et al*. (2007) reported an interesting brain PET scan study, comparing MCS patients with normal controls both before and after chemical exposure. They used substantial amounts of chemicals for this study, such that both normals and MCS patients showed changes in brain PET scans after chemical exposure, but different changes. Hillert *et al*. (2007) were exploring the hypothesis that the brains of MCS patients might be particularly active in processing odour exposure information in the brain. They found that, whereas two regions of the brain have higher levels of neural activation in response to chemical exposure in MCS patients, as compared with controls, the olfactory processing regions were less responsive in MCS patients vs. controls. So the changes in olfactory processing contradicted their prediction. The two regions showing higher chemically elicited activation in MCS patients were the anterior cingulate cortex and the cuneus-precuneus. The anterior cingulate cortex is part of the limbic system, so the view presented in the current review leads us to ask whether chemical exposure might be expected to produce increased neural sensitization in this region of the brain. The TRPV1 receptor is thought, as discussed above, to often act as a receptor for various organic solvents and related chemicals in MCS, leading one to ask whether the TRPV1 receptor is located in the anterior cingulate cortex. Steenland *et al*. (2006) have found that there are quite high levels of TRPV1 activity in the anterior cingulate cortex, consistent with a local activation by chemicals in this region of the brain. While it is quite possible that this interpretation is oversimplified, it provides us with an interpretation that is compatible with the NO/ONOO$^-$-cycle–neural-sensitization model of what may be happening in the brain to generate MCS-related chemical sensitivity. In any case, the observations of Hillert *et al*. (2007) provide us with an approach to developing a specific biomarker test for MCS-related changes in the brain.

A series of EEG studies have been published in which changes of EEG patterns in MCS patients have been reported in response to low-level chemical exposure, but where normal controls show little or no similar changes (Bell *et al*., 1999b; Bell *et al*., 2001•; Schwartz *et al*., 1994; Fernandez *et al*., 1999; Lorig *et al*., 1991; Lorig, 1994). These changes, which presumably reflect changes in neural sensitization in MCS, may well provide objectively measurable changes in response to chemical exposure. My own understanding of this area is distinctly limited, so I am unable to give the reader any insights as to the pros and cons of this approach.

Joffres *et al*. (2005) reported increases in skin conductivity in MCS patients, but not in normal controls in response to low-level chemical challenge. Interestingly these skin conductivity increases were more reproducibly linked to the blinded chemical exposures in MCS patients than were there self-reported symptoms. These responses are similar to the responses measured

in 'lie-detector tests'. The authors suggest that these responses to low-level chemical exposure may reflect a neural sensitization mechanism, indirectly influencing skin conductivity.

Kimata (2004) reported on changes in serum levels of four substances, comparing responses to low-level chemical exposures in normal controls, MCS patients and also in atopic eczema/dermatitis syndrome (AEDS) patients. The chemicals used were outgassed organic solvents in a recently painted room totalling between 3 and 3.5 $mg\,m^{-3}$. The four substances produced in response to chemical exposure were substance P (SP), vasoactive intestinal peptide (VIP), NG and histamine. The basal levels of SP, VIP and NG were elevated in MCS patients and these three, and also histamine, were elevated in the AEDS patients. These can all be viewed as inflammatory markers with SP, VIP and NG being linked to neurogenic inflammation, as suggested by Kimata (2004) and acting to increase mast-cell activation/degranulation and therefore increased histamine levels. All four of these increased in response to low-level chemical exposure in the MCS patients but *not* in either controls or in AEDS patients, although AEDS patients showed elevation of all four vs. normal controls. The increase of any of these in response to low-level chemical exposure may be useful as a possible specific biomarker test for MCS. The responses to low-level chemical exposure seem to be specific to MCS and are not produced by the inflammation seen in AEDS. Based on the data presented by Kimata, perhaps histamine may be the most interesting of these because the basal levels in MCS patients showed little, if any, elevation over normal controls, but low-level chemical exposure produced an almost doubling of these levels. These involve relatively simple serum testing, making these tests perhaps the most easily accessible in the clinical setting. One comment I have is that the data presented by Kimata (2004) show surprisingly consistent basal levels and also levels after chemical exposure from one MCS patient to another. One can't help wondering whether the patients studied here may have had MCS cases of very similar severity and it is possible that other cases with lowered severity may show lowered responsiveness.

Elberling *et al*. (2007) reported that basophils isolated from chemically sensitive patients responded to perfume exposure by releasing elevated amounts of histamine as compared with basophils isolated from normal controls. These results suggest that one can assay sensitivity even at the level of individual cells from sensitive individuals and that histamine release in response to chemical exposure may be a good assay for such sensitivity. It should be noted that the TRPV1 receptor is present on basophils (Planells-Cases *et al*., 2005), as are some other TRP receptors. It is possible, therefore, that sensitivity to chemicals mediated by these receptors might be expressed at the cellular level.

Peden (1996) reviewed studies of nasal lavage to provide objective measurement of irritant-induced nasal inflammation, including studies of multiple chemical sensitivity or sick-building syndrome. Such nasal lavage samples can be used to measure a large number of inflammatory markers, including inflammatory cytokines, NO, eicosanoid mediators, inflammatory neuropeptides and others. Some studies of this type were reported by Koren and Devlin (1992) and Koren *et al*. (1990; 1992), in which chemically sensitive people with rhinitis responses to chemicals reacted to such chemical exposure with increased measurable inflammatory markers in nasal lavage samples. These studies did not compare their results with those of normal controls without such rhinitis responses, but it would be surprising if there would be a similar inflammatory response in such people. Such controls were performed by Hirvonen *et al*. (1999), who showed that chemically sensitive people previously sensitized in a mould-infested building responded to mould exposure with increased inflammatory cytokines and increased NO production, unlike normal subjects, using nasal lavage to measure such responses. This is a good example of how nasal lavage may be used as an objective measure of sensitivity responses in 'sick-building syndrome' situations.

Interestingly, in a series of studies, Hirvonen *et al*. (1997a; 1997b) and Ruotsalainen *et al*. (1995) showed that one could show similar inflammatory responses to mould and other microbial materials in cells in culture, suggesting that such cell-culture responses could be used as a bioassay to isolate and identify materials from these organisms that produce such an inflammatory response.

In summary, these various objectively measurable responses to chemical exposure reflect three distinct predicted aspects of the $NO/ONOO^-$ cycle mechanism. The cough responses reflect a TRPV1 stimulation leading in turn to increased NMDA activity; several of the other tests presumably reflect neural sensitization responses; still others measure inflammatory responses. Many of these are likely to reflect local sensitivity, which may occur in some MCS patients, but not others. This is expected to be the case with the cough responses and nasal lavage measurements. So their possible role as specific biomarker tests may be expected to be limited to those having lung or upper respiratory tract impact, respectively.

As tests to be used in a clinical setting, perhaps the cough response to low-level capsaicin challenge, the nasal lavage tests, and the histamine and other responses studied by Kimata (2004) may be the most easily applied. One or more of these may be used, then, in a clinical context, to provide confirmation of MCS diagnoses initially based on the fit to an accepted case definition.

It is the author's opinion that the published studies suggest that we have a number of promising possible specific biomarker tests and it is essential, in my view,

that further research be done to establish some of these as specific biomarker tests for MCS to be used for both clinical diagnostic and experimental purposes.

XX.14 PATTERN OF EVIDENCE: FIT TO THE FIVE PRINCIPLES

The five principles underlying the NO/$ONOO^-$ cycle mechanism show how the cycle provides explanations for the wide variety of illness/disease properties. Where there is a good fit to each of the five, one can argue that a particular disease or illness is a good candidate for being caused by the NO/$ONOO^-$ cycle mechanism. In this sense, the five principles function collectively a bit like Koch's postulates. Having described much of the evidence above that is relevant to this issue of fit, it is time to summarize how good the fit is for each of the five principles in the case of MCS. I will not, in most cases, provide citations here, as they have been provided in the preceding sections of this review.

XX.14.1 Short-term stressors that initiate cases of multisystem illnesses act by raising NO synthesis and consequent levels of NO and/or other cycle elements

Each of the seven classes of chemicals implicated in initiating cases of MCS are known to act to increase NMDA activity and it is known that increased NMDA activity produces, in turn, increases in intracellular calcium, NO and $ONOO^-$. Elevated NMDA activity, intracellular calcium, NO and $ONOO^-$ are all elements of the cycle. It follows that there is an excellent fit to the first principle.

XX.14.2 Initiation is converted into a chronic illness through the action of vicious cycle mechanisms, through which chronic elevation of NO and $ONOO^-$ and other cycle elements is produced and maintained

This principle predicts that the various elements of the NO/$ONOO^-$ cycle will be elevated in the chronic phase of illness. Here we need to go through the various elements of the cycle to determine what evidence, if any, is available for their elevation in MCS.

There are numerous types of evidence for elevation of three closely linked elements of the cycle, NO, $ONOO^-$ and oxidative stress (Pall, 2007a; Pall, 2002; and see above):

- Several organic solvents implicated in MCS have been shown to produce increases in NO.
- Organophosphorus and carbamate pesticides, through their actions as acetylcholinesterase inactivators, can lead to increased muscarinic activity, which lead in turn to increased NO synthesis.
- Neopterin, a marker of increased iNOS induction (Pall, 2000; Pall and Satterlee, 2001), has been reported to be elevated in the more severely affected MCS patients (Bell *et al*., 1998c).
- Elevated NO has been found in several animal models of MCS and in two of these, it clearly has an essential role in producing the biological response.
- Elevated levels of 3-nitrotyrosine were found in several studies of an MCS animal model and 3-nitrotyrosine is a marker of $ONOO^-$.
- MCS, and the related conditions CFS and FM, have been treated by methods that greatly elevate hydroxocobalamin levels *in vivo*, and hydroxocobalamin is a form of vitamin B_{12} that is known to be a potent NO scavenger. The across-the-board improvement in symptoms suggests that NO has a role, either directly or indirectly, in generating the symptoms of these illnesses.
- It is known that $ONOO^-$ can produce a breakdown of the blood–brain barrier and such breakdown has been reported in both MCS patients and in an animal models of MCS.
- Several types of evidence implicate elevated NMDA receptor activity in MCS and and in related illnesses, including FM. Such elevated NMDA activity is known to produce increases in NO and $ONOO^-$.
- Oxidative stress has been reported in MCS patients (Ionescu *et al*., 1999; Lu *et al*., 2007), as well as in several animal models of MCS. The notion that oxidative stress is central to the pathophysiology of MCS was first explored by Levine (1983a; 1983b) 25 years ago.

There are three types of evidence suggesting that inflammatory cytokine levels are elevated in MCS:

- Nasal lavage studies of MCS patients have reported to have elevated inflammatory cytokine levels and elevated levels of other inflammatory markers.
- Several animal models of MCS have elevated inflammatory cytokines.
- While there have not been any systemic measures of inflammatory cytokines in MCS patients, to my knowledge, there have been multiple such studies of the related illnesses CFS and FM with reported elevations.

There are 13 distinct types of evidence implicating elevated NMDA activity in MCS; each of the seven classes of chemicals implicated in MCS can act by producing increased NMDA activity and there are also six additional types of evidence. These are all provided in Section XX.3 of this chapter.

Pall and Anderson (2004) listed 12 distinct types of evidence suggesting that elevated TRPV1 activity has roles in MCS. Ashford and Miller (1998) listed 10 striking similarities between MCS and neural sensitization, each of which can be viewed as evidence for neural sensitization in MCS; the animal model studies implicating neural sensitization provide an additional type of evidence. In addition, several of the putative specific biomarker tests, discussed above, provide support for a neural sensitization mechanism, providing a 12th type of such evidence.

Although there is extensive evidence for mitochondrial/energy metabolism dysfunction in CFS and FM, the only evidence for such dysfunction in MCS is from PET scan studies. Because the probe used in such PET scan studies is a glucose derivative, its transport and accumulation in the tissues is strongly impacted by mitochondrial dysfunction (Pietrini *et al*., 1998; Holthoff *et al*., 2004; Silverman *et al*., 2001).

In summary, although there have been no studies on either NF-κB elevation or BH4 depletion in MCS, to my knowledge, there are a total of 51 distinct published types of evidence supporting the role of one or more aspects of the NO/ONOO$^-$ cycle in the chronic phase of MCS. Given the paucity of research support that has been available for MCS research, that is a surprising amount of evidence!

XX.14.3 Symptoms and signs of these illnesses are generated by elevated levels of NO and/or other important consequences of the proposed mechanism, that is, elevated levels of ONOO$^-$, NO, inflammatory cytokines, oxidative stress, elevated NMDA, TRPV1 receptor activity and/or other aspects of the cycle

You have seen above and elsewhere (Pall, 2007a) that we can explain a wide variety of symptoms and signs of MCS through the NO/ONOO$^-$ cycle mechanism. While these proposed explanations are based on well-established mechanisms, their roles in MCS and related illnesses should be viewed as plausible, not established.

XX.14.4 Because the compounds involved, NO, superoxide and ONOO$^-$ have quite limited diffusion distances in biological tissues and because the mechanisms involved in the cycle act at the level of individual cells, the fundamental mechanisms are local

A local mechanism is supported in MCS and related illnesses basically from two distinct types of observations: The stunning variations in symptoms and signs of illness and in overall severity going from one MCS patient to another is difficult to explain without having a local mechanism that can have variable impact among the tissues of the body. Such tissue distribution can be directly visualized in the brain PET scan and SPECT scans studies, which show striking variations from one patient to another.

XX.14.5 Therapy should focus on down-regulating NO/ONOO$^-$-cycle biochemistry

There have been, unfortunately, few studies of therapy for MCS and except for one, these have been at the level of clinical observation and anecdotal reports, rather than clinical trials. The data we have available to ask for possible fit to the fifth principle are limited to the following:

- Clinical trial data on the related illnesses CFS and FM, where much more extensive data is available
- Evidence on causality from animal models of MCS
- A single clinical trial on MCS patients
- A variety of clinical observations and anecdotal reports.

The last of these is discussed in Chapter 15 of Pall (2007a) and will just be referred to here briefly.

Each of these types of observations provides evidence towards a fit to the fifth principle.

The animal model data that was discussed above provides evidence for causal roles of NO, TRPV1 activity and NMDA activity. Each of these types of studies have used agents that relatively specifically lower these activities and provide evidence, in the animal models, for what are, in effect, therapeutic effects of agents that down-regulate these specific aspects of the NO/ONOO$^-$ cycle.

There are quite a number of clinical trials with CFS and/or FM showing apparent efficacy of agents predicted to down-regulate various aspects of the NO/ONOO$^-$ cycle (**Table 4**). The citations for these clinical trials are provided in Chapter 15, Pall (2007a), except for the more recent trials. These recent trials are for pregabalin, a drug that indirectly lowers excitotoxicity, including NMDA activity (Mease *et al*., 2008; Crofford *et al*., 2005); D-ribose (Teitelbaum *et al*., 2006; Gilula, 2007); and the antioxidant *Ecklonia cava* extract (Bierman, 2008, see also In Focus, 2007).

As can be seen from **Table 4**, of these 16 classes of agents, many have antioxidant properties, providing evidence that oxidative stress has an important causal role in generating these illnesses. Some of these agents either act as NMDA antagonists, or act indirectly to lower NMDA activity, thus providing strong evidence for a causal role of excessive NMDA activity. Carnitine/acetyl carnitine, coenzyme Q10 and possibly hyperbaric oxygen are likely to act to help improve mitochondrial function, thus providing evidence for a causal role of mitochondrial/energy metabolism dysfunction.

The potent NO scavenger, hydroxocobalamin is a form of vitamin B_{12}, but its role is much more likely to involve scavenging NO. In a clinical trial study (Ellis and Nasser, 1973), there was no correlation between initial B_{12} levels and the clinical response. Furthermore, higher doses are needed to get clinical responses here than are needed to treat a B_{12} deficiency. It seems unlikely, therefore, that hydroxocobalamin is acting to allay a B_{12} deficiency. The potent action of hydroxocobalamin as a NO scavenger is sufficiently well established that hydroxocobalamin has been used in experimental settings to establish a role for NO in biological processes (Pall, 2001b).

There is also weaker evidence for two other aspects of the NO/ONOO$^-$ cycle having a causal role. The long chain omega-3 fatty acids in fish oil are well known to have anti-inflammatory aspects, so that their reported efficacy provides some evidence for an inflammatory causal role, although an alternative interpretation to these observations is also possible. High-dose vitamin C and high-dose folate supplements help restore BH4 levels, suggesting a causal role of BH4 depletion, but again, there are other possible interpretations for their actions, so the evidence for BH4 depletion being causal must be viewed as relatively weak.

There are a number of clinical observations suggesting that these same agents are often helpful in MCS treatment, suggesting a possible similar aetiology. The various types of evidence supporting an NO/ONOO$^-$-cycle mechanism for all three of these illnesses (Pall, 2006; Pall, 2007a; Pall, 2007b) of course also suggest a common aetiological mechanism.

The only relevant clinical trial on MCS patients is that of Heuser and Vojdani (1997), which used high-dose vitamin C therapy and showed objectively measurable improvements in immune function in response to therapy.

In chapter 15, Pall (2007a), I discuss five different protocols that have used multiple agents predicted to down-regulate different aspects of the NO/ONOO$^-$ cycle. Each of these five uses at least 14 agents/classes of agents. Two of these protocols have been tested in clinical trials, one (Teitelbaum's) with both CFS and FM patients and the other (Nicolson's) with CFS-like patients. Each of the five protocols appears to produce substantially better clinical responses than do single agents. This approach may, then, be promising as a general approach to the treatment of these illnesses. Of these, only the Pall/Ziem protocol has been tried on chemically sensitive patients and the generally favourable response to this protocol is described by Dr. Grace Ziem in that chapter.

Subsequently, the author has developed a somewhat different approach to nutritional support of these patients through the Allergy Research Group, containing 22 different agents/classes of agents predicted to down-regulate different aspects of the NO/ONOO$^-$ cycle. Physicians and others using this approach report favourable responses with a large majority of patients with CFS, FM or MCS. In some cases, people who have been ill for two or more decades report rapid improvements within three or four weeks, improvements that are sustained for periods of six months or more, but do not, in general, clearly progress towards complete recovery. Clearly, the reader needs to maintain a high level of scepticism, at this point. These are unpublished observations, they do not constitute anything approaching a clinical trial and the author has a conflict of interest here, receiving some royalties from the Allergy Research Group.

In summary, there are a number of types of evidence that provide some support for the view that agents that down-regulate various aspects of the NO/ONOO$^-$ cycle produce clinical improvement in patients with MCS and in related illnesses. However, there is a great need for much more clinical study of these approaches. Clinical trial data from the related illnesses, CFS and FM, provide substantial support for the view that oxidative stress, excessive NMDA activity and NO all have causal roles; less convincing evidence suggests that inflammatory biochemistry and BH4 depletion also have causal roles in these illnesses. Various aspects of the cycle also are reported to have causal roles in MCS animal models.

XX.15 PSYCHOGENIC CLAIMS

There have been a whole series of papers published arguing that MCS and/or the related multisystem illnesses are not physiological illnesses but are, rather, what has become known as psychogenic, having some often ill-defined psychological or psychiatric origin. These same authors have often argued that MCS should be called idiopathic environmental intolerance, a name that

Table 4. Clinical trial studies of agents predicted to lower NO/ONOO$^-$ cycle elements in the related illnesses chronic fatigue syndrome and fibromyalgia

Agent or class	Mechanism	Comments
Vitamin C (ascorbic acid)	Chain-breaking antioxidant; lowers NF-κB activity; reported to scavenge peroxynitrite and also help restore tetrahydrobiopterin (BH4) levels by reducing an oxidized derivative of BH4	May require high doses to be effective with the latter two mechanisms; this may be the basis of so-called 'megadose therapy' for vitamin C; clinical trials on CFS and MCS used high-dose IV ascorbate
Magnesium	Lowers NMDA activity and may be useful in improving energy metabolism and ATP utilization	Magnesium is the agent that is most widely studied and found to be useful in the treatment of the multisystem illnesses
Fish oil (long chain omega-3 fatty acids)	Lowers iNOS induction; lowers production of inflammatory eicosonoids; important for brain function	Highly susceptible to lipid peroxidation and may, therefore be depleted; four studies reported improvements in clinical trials, three with CFS and one with FM
Flavonoids	Chain-breaking antioxidants; some scavenge peroxynitrite, some scavenge superoxide; some reported to induce superoxide dismutase (SOD); All three types are found in FlaviNox; some flavonoids may also act to help restore BH4 levels; lower NF-κB activity	Ginkgo extract tested in CFS; anthocyanidin flavonoids in FM; other flavonoids tested in CFS animal model
NMDA antagonists	Lower NMDA activity	Four different antagonists reported to be effective in the treatment of fibromyalgia; anecdotal reports of effectiveness for MCS
Agents that indirectly lower excitotoxicity including NMDA activity	—	Only clinical trials done with pregabalin for fibromyalgia, but other members of this class often used clinically
Acetyl L-carnitine/carnitine	Helps transport fatty acids into mitochondria; may be important here not only directly for energy metabolism but also to restore the oxidized fatty acid residues that may be produced in the cardiolipin of the inner membrane	May also help lower reductive stress; two trials in CFS
Ecklonia cava extract	Polyphenolic chain-breaking antioxidant; reported to help scavenge both peroxynitrite and superoxide; based on its reported properties, it may also help restore BH4 levels	Appears to stay in the body much longer than do the flavonoids, a useful property; reported to be helpful in a clinical trial study of fibromyalgia
Reductive stress relieving agents	These include S-adenosyl methionine (SAM or SAMe), trimethylglycine (betaine), carnitine and choline	SAM reported to be effective in multiple clinical trials with FM and CFS patients; betaine widely used clinically
Hydroxocobalamin form of vitamin B-12	Potent nitric oxide scavenger, lowers nitric oxide levels	Limited intestinal transport; often taken by intramuscular injection or as a nasal spray or inhalant; clinical trial with CFS-like illnesses; widely used for treatment of CFS, FM and MCS
Folic acid	Relatively high doses will lower the partial uncoupling of the nitric oxide synthases by helping to restore tetrahydrobiopterin (BH4)	Reacts with oxidants and therefore may be depleted due to the NO/ONOO$^-$ cycle

Table 4. (*continued*)

Agent or class	Mechanism	Comments
Algal supplements	Probably act as antioxidants	—
Hyperbaric oxygen	May act to help restore cytochrome oxidase activity by competing with nitric oxide	My impression is that this approach needs to be used with substantial care—too high or prolonged dosage can cause damage
Trimethyl glycine (betaine), S-adenosyl methionine (SAM), choline, carnitine	Lower reductive stress; also helps with the generation of S-adenosyl methionine (SAM)	While lowering reductive stress may be the main concern, SAM generation may also be of concern; the enzyme methionine synthase is inhibited by nitric oxide and inactivated under conditions of oxidative stress, thus leading to lowered SAM and lowered methylation
Coenzyme Q10 (ubiquinone)	Important in mitochondrial function; important antioxidant, especially in mitochondrion; reported to scavenge peroxynitrite	Optimal dosage may vary considerably among different individuals; suggest taking early in day
D-ribose, RNA or inosine	Two important functions: Provides adenosine for restoring adenine nucleotide pools after energy metabolism dysfunction; when catabolized, the purine bases generate uric acid, a peroxynitrite scavenger	Each of these may act somewhat similarly; however only D-ribose has been tested in a clinical trial and reported to be effective; each of these agents has distinct drawbacks

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denies, in effect, that chemicals cause MCS or have a role in eliciting symptoms in people who suffer from MCS. It also denies that we have a mechanism that may explain the many puzzling features of MCS. The name implies that we have neither initiating causes nor ongoing causes of illness.

What this section does, is to briefly and superficially review this field, making many generalizations, some of which may not be adequately supported. To do a thorough review would take a paper considerably longer than this entire chapter, so there is not space nor time to do so. The reader is referred to Chapter 13 in Pall (2007a), which provides a more comprehensive discussion of this area, not just for MCS, but also for CFS and FM. The reader is also strongly encouraged to look at the papers advocating a psychogenic basis for MCS (**Table 5**) and the Davidoff and Fogarty (1994), the Davidoff *et al*. (2000) and the McCampbell (2001) reviews.

From a toxicological perspective, none of these psychogenic advocate papers considers the question of what chemicals are apparently involved in MCS and how they might act as toxicants in the human body. From a toxicological perspective, therefore, they all must be viewed as being flawed. This section outlines the main issues with regard to psychogenesis of MCS that were developed in Chapter 13 in Pall (2007a) and then discusses several of the reviews that have each been written from a psychogenic perspective.

There are, in the author's view (Pall, 2007a), 10 important issues that challenge the positions of psychogenic advocates of MCS and related multisystem diseases and we are considering these here one at a time.

Many such advocates argue that these multisystem illnesses are caused by 'belief' and that they are somatoform disorders generated by a mechanism called somatization. How well founded are these views? Let's consider the basis of somatoform disorders and somatization.

Somatoform disorders are defined (Smith, 1990) as a group of disorders with somatic symptoms that suggest a physical disorder, but for which no organic aetiology can be demonstrated. There is presumptive evidence of a psychological basis for the disorder.

Somatization is defined as a process whereby psychological distress is expressed in physical symptoms (Smith, 1990). So psychogenic advocates typically argue that MCS and the other multisystem illnesses are somatoform disorders generated by the process of somatization. According to its definition, it is incumbent on such psychogenic advocates to demonstrate that *no organic aetiology can be demonstrated*. That is, they not only need to show that no organic aetiology *has* been demonstrated but that none *can* be. This is a very difficult hurdle for them and none of them, to my knowledge, have even tried to jump it. They rarely, if ever, consider the detailed properties of the mechanism proposed here, or the neural sensitization interpretation or the neurogenic inflammation interpretation, nor have they developed a

Table 5. Publications of MCS skeptics

Gots (1996)	Argues for a psychogenic 'mechanism' for MCS based mainly on dualistic reasoning
Barsky and Borus (1999)	Argues the multisystem illnesses are 'functional somatic syndromes'. Unclear whether this argues for psychogenesis, but paper is often cited by those advocating psychogenesis
Kellner (1994)	Argues that multisystem illnesses are somatoform disorders caused by somatization
Staudenmayer (1999)	Staudenmayer's book makes the longest argument for psychogenesis in MCS
Wessely *et al*. (1999)	Argues that the multisystem illnesses may not be distinct and may share an aetiology possibly centred on psychogenesis
Binder and Campbell (2004)	Similar arguments to Gots (1996), Kellner (1994) and Staudenmayer (1999); considers a broader group of illnesses
Staudenmayer *et al*. (2003a)	Goes through the Hill criteria, asking whether MCS (IEI) can be a physiological illness caused by chemical exposure.
Staudenmayer *et al*. (2003b)	Goes through the Hill criteria, asking whether MCS (IEI) can be a psychogenic illness
Wiesmüller *et al*. (2003)	Another proposal to the effect that these multisystem illnesses may be somatization disorders. While considering these illnesses from a predominantly psychiatric perspective and ignoring physiological, biochemical and animal model data, the authors are much more circumspect about their inferences than are the psychogenic advocates
Hausteiner *et al*. (2007)	A psychiatric interpretation of MCS or what they call IEI.
Eis *et al*. (2008)	Complex psychological study; argues against physiological interpretations while providing no data on them
Das-Munshi *et al*. (2006)	Review of provocation studies in MCS
Das-Munshi *et al*. (2007)	Review of MCS, from a group of psychogenic advocates from the Institute of Psychiatry, Kings College, London

compelling argument ruling out *any possible organic aetiology*.

While it may be argued that they have never even attempted to seriously fulfil this requirement, it is also the case that the very concepts of somatoform disorders and somatization have come under increasing attack (Janca, 2005; Epstein *et al*., 1999; Mayou *et al*., 2005; Dalen, 2003; Bradfield, 2006; Sykes, 2006). There are a number of reasons for this, including the issue that the concept of somatoform disorders and somatization is based on a dualistic view of human beings, where the psychological/psychiatric/mental is separate and distinct from the biological/physiological/physical. The process of somatization assumes that all of the initial causes are on one side of this dualism and somehow reach across the divide to generate physical symptoms. However this Cartesian dualism has been rejected by modern science. For example the American Psychiatric Association (1994) states that 'there is much "physical" in "mental" disorders and much "mental" in "physical" disorders'. Dualistic reasoning has been used repeatedly by advocates of psychogenesis of MCS and other multisystem illnesses and has led them astray in many circumstances. Let us consider an example: a letter published by Black (2002) on the apparent effectiveness of the drug paroxetine in the treatment of MCS. Paroxetine has been shown to lower NOS activity (reviewed in Chapter 6, Pall, 2007a) and is also a serotonin reuptake inhibitor and is a drug that has been used to treat certain psychiatric disorders. Black reports that this drug was effective in the treatment of an MCS patient and in other studies, in two other patients and concludes that, 'This case joins two others in showing *that some patients diagnosed with multiple chemical sensitivity have an underlying psychiatric disorder that, when identified, responds to medication therapy'* (italics added). Black concludes that because paroxetine has been effective in the treatment of some psychiatric diseases, it must be acting to correct a psychiatric flaw in these MCS cases. This is the same logical flaw as if one were to argue that: aspirin cures headaches; aspirin decreases blood clotting; therefore headaches cause blood clotting. The logical flaw here is obvious, but because Black is so immersed in an assumed dualism, he cannot apparently see it. I will provide some additional examples of such dualistic reasoning below.

We have discussed, thus far in this section, three weaknesses that show up in the positions of psychogenic advocates of MCS: that they base their arguments on the concepts of somatoform disorders and somatization, concepts that they have never shown to be adequately supported in MCS and concepts that have been attacked on a theoretical basis as well; that much of their position is based on a rejected dualism between the mental/psychiatric/psychological on the one hand and the physical/biological/physiological on the other; and that this rejected dualism has led them, in turn, to make

logical flaws. These, then are three substantial flaws underlying psychogenesis—there are others.

Another important issue is that there is a long history of false psychogenic attribution in medicine. In Chapter 13 (Pall, 2007a), there is a discussion of the fact that each of the following diseases has been falsely claimed to have an aetiology that is largely or completely psychological:

1. Multiple sclerosis (MS)
2. Parkinson's disease
3. Lupus
4. Interstitial cystitis
5. Migraine
6. Rheumatoid arthritis
7. Asthma
8. Gastric and duodenal ulcers
9. Ulcerative colitis.

Each of these has been subsequently been shown to be a real physiological disease. Of that list, the psychogenic claim that has been most recently rejected by modern science is number 8, ulcers, for which two Australian physicians, Robin Warren and Barry Marshall won the 2005 Nobel prize in physiology and medicine for showing that the bacterium *Helicobacter pylori* plays a key role in the development of both types of ulcers. Ulcers are a bacterial infectious disease, with ulcers being generated when the inflammation produced by a *Helicobacter pylori* infection becomes sufficiently severe. Ulcers can be treated by a simple antibiotic regimen and this is not a psychogenic illness, as had been confidently claimed for decades.

It is essential, in the author's view, that psychogenic advocates of MCS or other multisystem illnesses show that they are not repeating the same errors that led to false psychogenic claims in the past. However, none of them has ever apparently considered this issue in their publications.

A fifth issue is the role of genetics in dealing with susceptibility to MCS or other multisystem illnesses. There is substantial published evidence for a role of genetics in determining such susceptibility, not only in MCS, but also with CFS, FM and PTSD. The role of specific genes in MCS provides strong support for the inference that chemicals are acting as toxicants in MCS and the role of the CCK-B gene also provides some evidence for a role of the NMDA receptors. Thus the genetic evidence is in very good agreement with the mechanism discussed in this review. The genetics of CFS is also consistent with a $NO/ONOO^-$ cycle mechanism (Chapter 5, Pall, 2007a). But there is a more fundamental issue with a genetic role. Genes act by influencing the structure and amounts of proteins synthesized in the body and by doing so, determine both the physical structure of the body and its biochemical activities. In a dualistic framework, they act to determine the biology and any psychological effect is indirect, produced from the biology. Staudenmayer (1999, p. 20) states that, 'The core supposition of psychogenic theory is that psychological factors are *necessary and sufficient* to account for the clinical presentations of EI [what he calls MCS] patients. Psychogenic theory emphasizes belief, somatization, psychophysiologic stress and anxiety responses, and psychogenic etiology' (italics added). Obviously if psychological factors are *necessary and sufficient*, then there is no room for a genetic role, or for any other biological role. The demonstrated genetic roles in MCS and other multisystem illnesses show that psychological factors are *not* sufficient.

A sixth issue is that psychogenic advocates rarely make clear, testable predictions. The Staudenmayer prediction discussed in the previous paragraph is a rare, perhaps unique, exception to this and as indicated immediately above, the test leads to rejection of the psychogenic hypothesis. The need to make clear, testable (and therefore potentially falsifiable) predictions is essential in science. One of the things that they do, however, is to suggest that because some (but not other) patients with multisystem illnesses clearly suffer from what are classified as psychiatric symptoms, that therefore the multisystem illnesses should be viewed as psychiatric. However, there is a large amount of literature showing that most, perhaps all, serious chronic diseases are characterized as having comorbid psychiatric symptoms, but that does not mean that these serious chronic diseases are psychiatric. The fact that cancer patients and rheumatoid arthritis patients have higher prevalences of PTSD, anxiety and depression, for example, does not make either cancer or rheumatoid arthritis a psychiatric disease.

A seventh issue is that scientists have an obligation to avoid emotion-laden rhetoric and to attempt to provide objective assessments of the scientific literature. Some examples of such emotion-laden statements from the psychogenic advocates are provided elsewhere (Chapter 13 in Pall, 2007a) and will not be repeated here. The focus here is on the need to provide an objective assessment of the literature. Let us consider some specific examples.

The Binder and Campbell (2004) review has relatively brief discussions of several illnesses, including MCS, CFS and FM with relatively few citations provided for each of them. They argue that in these illnesses, cognitive abnormalities are not caused by neurological disease, but rather are caused by 'biological and psychological factors', while concentrating their claims heavily on the psychological side. It is probably reasonable to expect that the relatively few citations on each illness will be carefully chosen to represent some relatively objective assessment of the relevant literature. Let's take a look at some of them here.

On p. 371, Binder and Campbell (2004) argue that the proposed name change from CFS to chronic fatigue and immune dysfunction syndrome was made 'despite the lack of evidence of immune dysfunction in this illness'.

The only citation provided is that of the psychiatrist and psychogenic advocate Wessely (1997). They would apparently have us believe that the extensive evidence for immune dysfunction in CFS, reviewed, for example, by Komaroff and Buchwald (1998), by Patarca (2001) and by Klimas and Koneru (2007), does not exist because one psychogenic advocate argues that it does not.

In the MCS section of their paper, Binder and Campbell claim that the substances triggering discomfort in people with MCS are 'aromas rather than neurotoxins', citing the psychologist Bolla (2000) as their only documentation for this. They would apparently have us believe that the hundreds of citations showing that organic solvents are neurotoxicants that are cited in Kilburn (1998) or that the many citations showing that pesticides are neurotoxicants cited earlier in this chapter do not exist.

Binder and Campbell (2004) also state that sensitization 'may be initiated by aversive childhood experiences such as sexual abuse', providing Bell *et al*. (1998b) as their only documentation. What Bell *et al*. (1998b) actually report is that girls with a history of sexual abuse were at apparently greater risk for later becoming chemically sensitive, not that it directly initiated cases of MCS. But what is much more important is that they cite this one study as evidence for a possible causal role of sexual abuse in MCS, while completely ignoring the many dozens of studies showing an apparent causal role for chemical exposure in initiation of cases of MCS—and chemical exposure often leads very quickly to the development of MCS symptoms—as compared with the possible role of sexual abuse as a risk factor in the medical history of the patient. This is, unfortunately, a typical example from the psychogenic literature of only citing evidence that can be interpreted as supporting their viewpoint, while completely ignoring massive literature that contradicts it.

Binder and Campbell (2004) also dismiss a number of physiological changes found in MCS and other multisystem illnesses based on these same changes being found in what are classified as psychiatric diseases. For example they state that, 'Neuroendocrine abnormalities are associated with FM and that the illness is caused by abnormal sensory processing. *However emotional problems also are associated with neuroendocrine disorders. We know of no evidence of neuroendocrine abnormalities specific to that condition.* There was evidence of reduced cerebral blood flow in the thalamus and pontine tegmentum in patients with FM, *but similar findings are nonspecific and occur in psychiatric patients*' (italics added). It should be noted that, as discussed above, similar neuroendocrine abnormalities are also reported in FM and CFS, as well. Later in the same paper they state that, 'A fluorine [sic]-deoxyglucose PET study suggested that hypometabolism of the brain stem was found only in CFS and not in depression, *but a study using the same technique found no differences between a group with CFS and a group with somatization disorder*' (italics added). Again similar brain changes are reported in MCS and CFS, albeit with different tissue distribution. In both of these quotes, Binder and Campbell (2004) dismiss any biological significance of objectively measurable physiological changes in these multisystem illnesses, if similar changes are also reported to occur in psychiatric diseases. By their dualistic reasoning, if a physiological change occurs in a psychiatric disease it is forever dismissed as a biologically significant marker in other illnesses, based on some sort of guilt by association. The obvious inference that when these changes are seen in a psychiatric disease, they are important clues as to the pathophysiology of that disease seems to be completely lost on them.

The dualistic reasoning seen with Binder and Campbell is all too common in the psychogenic literature. The Black (2002) letter with its dualistic reasoning is discussed above. Gots' (1996) paper on MCS is essentially all based on such dualistic reasoning. In it he states, 'Stimulation of a neurotransmitter or release of a hormone occurs in response to stimulus. Evidence of response to stress or phobia, such as EEG changes or elevated cortisol levels, helps to describe part of the organic interface between stimulus and response and supplements our knowledge of how the mind produces symptoms. *These responses, however, are not indicative of organic dysfunction and do not eliminate the role of the mind in the phobic or stress response*' (italics added). The author noted (Chapter 13, Pall, 2007a) that, 'Gots would have us believe that because these are produced in response to psychological stress, cortisol or EEG changes are of no organic consequence, incapable of producing organic dysfunction. Taken to its logical conclusion, this same reasoning would have us believe that if a person responds to psychological stress by committing suicide, he or she is not "organically" dead.' Elsewhere in his paper Gots (1996) makes clear where some of his commitment to this discarded dualism comes from stating that, 'Manufacturers cannot be held responsible for responses that depend on psychological processes'. The legal issues of possible liability for the initiation of MCS cases are often discussed in the papers of psychogenic advocates and they consistently argue against any such liability. Could that be related to their roles as 'expert witnesses' in such liability trials?

In a recent MCS review, Das-Munshi *et al*. (2007), referring to a study by Baines *et al*. (2004), stated that 'a recent study suggested that people with MCS showed a nonsignificant trend towards lymphocyte depletion, but this is also known to occur in major depression, possibly as a result of hypercortisolaemia, and widespread immunological differences have also been shown in people with somatization disorders'. In that one sentence they state that the trend towards lymphocyte depletion in MCS patients was nonsignificant, whereas Baines *et al*. (2004) reported it was highly significant ($p<0.001$);

they also discount the biological significance of this by suggesting that because similar changes occur in two apparent psychiatric diseases, major depression and somatization disorders, this aberration has no biological significance in MCS. So we see again, dualistic reasoning discounting any objective physiological changes if they occur in what are considered to be a psychiatric diseases. There is a third flaw in this sentence—that in what is *not* said. This statement, when coupled to the lack of any discussion of other objectively measurable changes in MCS, suggests that lymphocyte depletion is the only such reported change, when clearly it is not.

One of the papers that was reviewed in Chapter 13 on psychogenesis of Pall (2007a), was a paper by Staudenmayer *et al*. (2003a) raising the issue of whether chemical exposure meets the Hill (1965) criteria for initiation of cases of MCS. Hill, in his paper, stated nine criteria that were proposed to be used to help determine whether a particular environmental stressor or group of stressors might have a causal role in the initiation of some particular illness or disease. The goal here is to distinguish chance association with causation. The idea was not that all of them had to be fulfilled in order to infer probable environmental causation, but that if there was reasonably good evidence for most of them, one might infer such causation. So the question that needs to be raised in the context of MCS is whether chemical exposure is apparently causal in initiating cases of MCS, based on the Hill criteria. This seemed to be an interesting paper to analyse because Ashford and Miller (1998), themselves did an analysis of the Hill criteria as it applies to MCS (pp. 273–276), so it would be interesting to see how Staudenmayer *et al*. (2003a) might deal with these questions. Staudenmayer *et al*. (2003a) concluded (p. 244) that 'toxicogenic theory fails to meet any of the nine Hill criteria'.

The Staudenmayer *et al*. (2003a) paper is surprising in three ways: firstly they were apparently unaware of the previous Ashford and Miller (1998) treatment of this same topic in their very influential book. Secondly Staudenmayer and colleagues either did not know about or did not see the relevance of any of the cited literature that Ashford and Miller (1998) used to support their view that there was substantial evidence for fulfilling six of the nine Hill criteria with regard to chemical causation of MCS. Thirdly, in several cases, Staudenmayer failed to even ask the question that Hill requires them to ask in supposedly examining the case for the nine Hill criteria. Let's go through the first four Hill criteria one at a time to see how the Staudenmayer *et al*. (2003a) treatment compares with the scientific literature that appears to be relevant to these Hill criteria.

The first Hill criterion is strength of association. In this case, is exposure to the types of chemicals suggested to have a role in causing MCS associated with increased incidence of MCS? There are three main types of evidence suggesting such a relationship (Pall, 2007a, pp. 218–220). Firstly, there is the great increase in synthetic organic chemical production (15-fold increase from 1945 and 1980) and also a roughly similar increase in the production of pesticides, following World War II through the 1980s, paralleling the apparent incidence of MCS. One has to say apparent because we have no good epidemiological data before 1980, so we have to rely on surrogates, such as the increasing scientific and medical interest in this field around the world, as possible measures of increased MCS incidence. Secondly, we have the great increase in 'sick building syndrome' situations in the USA following the decreased requirement for indoor air flow that was put into place in 1973, after the first oil shock. By the late 1980s the US Environmental Protection Agency was reporting that fully 50% of the environmental complaints that they had to deal with were 'sick building syndrome' types of complaints (much of this information comes from Ashford and Miller, 1998 and is discussed in Pall, 2007a, pp. 218–220). So we have an apparent parallel, both with regard to increased chemical production and decreased air flow, and apparent increased MCS initiation. A third example is the genetic evidence that genes that determine the rate of metabolism of chemicals can influence the prevalence and therefore incidence of MCS. The only study that was available before Staudenmayer *et al*. (2003a) submitted their paper was the Haley *et al*. (1999) study on PON1, but there is, as discussed above, much more data available now. Staudenmayer *et al*. (2003a) state that there is no evidence for increased incidence of IEI (what they call MCS) with occupational chemical exposure; this is not accurate because Zibrowski and Robertson (2006), McKeown-Eyssen *et al*. (2001) and Maschewsky, (1996; 2002) present some data on this, as discussed above, but it is fair to state that we have very limited data. There is extensive data both on the existence of occupational asthma and the role of chemical exposure in it, and that it is part of the MCS spectrum of sensitivity, but clearly Staudenmayer *et al*. (2003a) are unable or unwilling to see that connection. Staudenmayer *et al*. (2003a) spend most of their discussion on what is supposed to be the first Hill criterion criticizing the prevalence data on MCS, rather than asking the question that must be asked for this Hill criterion—is there an association of chemical exposure with MCS incidence and prevalence, however those may be defined. In the author's judgement, the evidence for the first Hill criterion in the case of chemical causation of MCS is suggestive, but not compelling, with the exception of the more recent genetic evidence, which was not published before the Staudenmayer *et al*. (2003a) paper was submitted. However, to state, as they did, that there is no such evidence is simply incorrect.

The second Hill criterion is consistency: is there a fairly consistent illness or disease pattern that has been described in a variety of different places and circumstances? Similar observations have been made in a variety of countries around the world, including the USA,

at least nine European countries, Canada, Australia and Japan. As stated by Miller (1997, p. 445) 'numerous investigators from different geographic regions have published strikingly similar descriptions of individuals who report disabling illnesses *after exposure to recognized environmental contaminants*' (italics added). What Staudenmayer *et al*. (2003a) discuss regarding the consistency criterion is whether or not chemical provocation studies in MCS have been properly performed, ignoring the central issue raised by the second Hill criterion.

The third Hill criterion asks whether there is some specificity to the stressors proposed to initiate a specific disease or illness. Here, Staudenmayer *et al*. (2003a) produce the strongest of their arguments with regard to any of the Hill criteria. The chemicals apparently involved have appeared to have little specificity and many of the case definitions, as seen above, discuss them as being 'unrelated' chemicals. There had been only four papers that had been published before the Staudenmayer *et al*. (2003a) paper had been submitted proposing that chemicals might act via increased NMDA activity and/or increased NO and $ONOO^-$, so perhaps it is not unreasonable that they did not consider that possibility. At this point in time, however, it should be clear that there is a substantial argument for specificity through the common response mechanism of NMDA stimulation, even though diverse chemicals are implicated in MCS initiation and in eliciting symptoms in those already sensitive.

The fourth Hill criterion, that of temporality asks, in the context of MCS, whether chemical exposure precedes or follows the initiation of illness. In Chapter 13 of Pall (2007a), the author led the reader to 30 citations that reported that chemical exposure preceded illness initiation, all apparently published before the submission of the Staudenmayer *et al*. (2003a) paper and there are a dozen additional such citations provided in Section XX.2 of this review; none of these 42 are cited by Staudenmayer *et al*. (2003a) in what they describe as an 'evidence-based review'. These 42 citations are not a comprehensive list of the literature and there are likely to be many other such publications as well. Among the papers ignored by Staudenmayer *et al*. (2003a) is the highly cited Miller and Mitzel (1995) paper, whose title alone implies that it is relevant to this fourth Hill criterion. How do Staudenmayer *et al*. (2003a) support their contention? They cite a single non-peer-reviewed paper by a psychogenic advocate, Terr (1993), published some 10 years earlier; the Terr paper criticizes people studying the physiological basis of MCS, based on their theoretical models and their methodology for studying the effects of chemical exposure on MCS patients. The Terr (1993) paper is, therefore, irrelevant to the issue of temporality—does chemical exposure precede or follow the initiation of illness. The Terr (1993) paper also refers to MCS as if it were an allergy, which clearly it is not.

It is difficult to see how any objective assessment of the literature can come to the conclusion that the fourth Hill criterion is not supported for MCS and the failure of Staudenmayer *et al*. (2003a) to even consider the easily accessible, extensive and obviously relevant scientific literature may be viewed as a sign of their unacceptable bias.

There is not time time nor space here to go through the other five Hill criteria as they relate to MCS, but the reader is referred to the discussion of this in Chapter 13 of Pall (2007a). The reader is also encouraged to read both the original Hill (1965) paper and also the Staudenmayer *et al*. (2003a) paper. The author's own assessment of the Hill criteria is that there is strong evidence for fulfilling six of the Hill criteria for MCS and weaker, but still suggestive, evidence for fulfilling the other three (Chapter 13, Pall, 2007a). Such evidence is not immune from criticism. It is common, as Hill (1965) suggests, that such evidence can be questioned and it is for that reason that it makes sense to weigh the evidence on nine criteria, rather than just a few, to assess the balance of evidence in the complex consideration of possible environmental causation. It is not necessary, according to Hill (1965), to find support for fulfilling all of the nine criteria in order to make a substantial case for environmental causation, but it is the author's view (Chapter 13, Pall, 2007a) that one can do just that for chemical causation of initiation of MCS cases.

Before leaving the issue of possible psychogenesis of MCS, it is essential to discuss the two masked, placebo-controlled provocation (that is controlled-exposure) studies that have been published, which together, to my knowledge, provide the only evidence that is reasonably claimed to positively argue for a psychogenic aetiology of MCS. Although there are only two such studies, given the relative paucity of direct experimental studies on MCS, it is important to look at them carefully. Both of these report on studies where they performed placebo-controlled provocation studies where the exposures were 'masked' by the presence of a presumably benign masking agent, so that the patients would be unable to tell through odour when they were exposed to the chemical. In both studies, the patients were presumably unable to distinguish the chemical exposure from the masking agent alone. One of these studies was published by Staudenmayer, Selner and Buhr (Staudenmayer *et al*., 1993) and the other was published by Smith and Sullivan (2003). Both were reviewed favourably by Das-Munshi *et al*. (2006), a group that has argued for a psychogenic mechanism of MCS and also other multisystem illnesses (Das-Munshi *et al*., 2006; Das-Munshi *et al*., 2007).

The Staudenmayer *et al*. (1993) study has been criticized for three reasons (Miller, 1997; Bell *et al*., 1997; Bell *et al*., 1999a; Joffres *et al*., 2005): the masking agent used, a heavy amount of mint, is not always benign for MCS patients (Fernandez *et al*., 1999) and therefore may not be the neutral masking agent that the authors claim; MCS patients can become desensitized when exposed

to various chemicals and these experimenters failed to provide the patients with a substantial period away from such exposures before the provocation challenges were performed; and the patients were not chosen using a standard case definition of MCS, so that there is some question whether they were, in fact, MCS sufferers.

Somewhat surprisingly, the more recent Smith and Sullivan (2003) study may have had somewhat similar problems. Smith and Sullivan tested CFS patients, not MCS patients, and although there is a substantial comorbidity between the two, they did not use, as one would argue they should have, MCS patients who fulfilled a well-accepted case definition for MCS. They do report that their patients had self-reported food sensitivities or chemical sensitivity or both, but food sensitivity is not specific for MCS and is common among CFS patients with no apparent chemical sensitivity. Smith and Sullivan (2003) chose the chemicals to be used as follows: chemical substances chosen by an allergist based on 'clinical criteria and patients subjective responses' were previously tested on each patient until a 'reactive substance' was identified. They give trichloroethane as an example of such a reactive substance, but provide no further information on the chemicals used in this study or their frequencies of use and very little information on dosage. The masking substance used was identified as a substance to which the participants did not react—they give vanilla essence as an example, but do not provide any further information on the masking compounds used. It has been reported that vanillin, the main odourant in vanilla essence, is more of an irritant in MCS patients than in normal controls (Hillert *et al*., 2007), suggesting that it is not a neutral masking agent for MCS patients. Clearly if either the original test of the 'reactive substance' was a false positive or if the test of the possible masking compound was a false negative, the experimental test for that specific patient would have been flawed.

There is no description of any procedure being used in Smith and Sullivan (2003) to prevent desensitization of patients, caused by recent chemical exposures prior to provocation, another possible criticism. The choice of CFS patients rather than MCS patients can be criticized for an additional reason. Classical MCS patients have their symptoms resolve in the absence of chemical exposure, whereas CFS patients do not. Because they used neuropsychological tests to measure reactions here, CFS patients will have at best a low signal-to-noise ratio because of the high level of neuropsychological aberrations before any provocation exposure. Therefore, these patients were not well chosen, in my judgement, for use in such a test, even if they all did have comorbid MCS.

It should be clear that these provocation challenge experiments are complex and difficult to perform with anything approaching a bullet-proof protocol. The point here is *not* that these two experiments are flawed and that all of the experiments that support the conclusion that MCS patients react to low levels of chemicals acting as toxicants have no flaws. Rather it is that we need to maintain a high level of objectivity in analysing these complex experiments. When Das-Munshi *et al*. (2006) conclude that the Staudenmayer *et al*. (1993) and Smith and Sullivan (2003) studies have no flaws, but that all of the studies coming to the opposite conclusion have substantial flaws, their objectivity must be questioned.

XX.16 SUMMARY OF THIS WHOLE AREA OF POSSIBLE PSYCHOGENESIS OF MCS AND OTHER MULTISYSTEM ILLNESSES

- Psychogenic advocates have failed to consider how chemicals implicated in MCS may impact the human body and specifically the human brain.
- They have failed to consider animal models of MCS and what lessons they may carry on the mechanisms of MCS.
- They have failed in most instances to provide anything resembling an objective assessment of the scientific literature about MCS. Given that most psychogenic advocates have clear conflicts of interest, either making large amounts of money testifying as 'expert witnesses' in MCS liability trials or as psychiatrists who may make substantial amounts providing psychiatric treatment for patients with multisystem illnesses, their ability or lack of same to provide an objective assessment of the literature must be subject to careful scrutiny.
- Their interpretation of MCS and other multisystem illnesses is dominated by the view that these illnesses are produced by the beliefs of the patients and that these are somatoform disorders generated by a process called somatization. However, they have failed to provide evidence that there cannot be a physiological explanation for MCS and the basic concepts of somatoform disorders and somatization have come under increasing attack.
- Their approach to MCS and other multisystem illnesses is based on the rejected dualism between the mental/psychological/psychiatric and the physical/biological/physiological.
- Belief in that dualism has apparently led them to make many logically flawed arguments.
- There is a long history of false psychogenic attribution in medicine, making it essential that psychogenic advocates show that they are not simply repeating the errors of the past. They have failed to consider this issue.
- Their argument that psychological factors are necessary and sufficient to explain MCS and other multisystem illnesses is falsified by the genetic data;

both the specific genes implicated in MCS and their known function provide for such falsification, but also the general finding that genes have a role in determining susceptibility implicates biological factors because genes act by determining the structure and biochemical activities of the body.

- Psychogenic advocates rarely make clear and testable predictions. One of the rare exceptions to this is clearly falsified by the available data.
- Their papers are full of emotion-laden statements.

Each of these ten considerations creates, in my judgement, great challenges for psychogenic advocates of MCS. Clearly the combination of all ten create still more daunting challenges, completely apart from the main thesis of this review on the NO/ONOO$^-$ cycle and the physiological mechanism(s) of MCS.

XX.17 SUMMARY AND AREAS OF GREATEST RESEARCH NEED

This chapter describes a detailed apparent mechanism for MCS, called the NO/ONOO$^-$ cycle, which explains, when fused with neural sensitization, neurogenic inflammation and other mechanisms, the many challenging aspects of this illness that have never been explained previously. Because new scientific paradigms are tested, often largely, by their ability to explain the many previously unexplained aspects of a scientific field, the power of the NO/ONOO$^-$ cycle as an explanatory model is of great importance. It is my view that the power of the NO/ONOO$^-$ cycle mechanism, when fused with the earlier neural sensitization mechanism as an explanatory model in MCS, and the various aspects of the model that are well supported experimentally, support the inference that the overall model is likely to be fundamentally correct. However, it could certainly be wrong in one or more details and is almost certainly incomplete.

This proposed mechanism is supported by well-established mechanisms of action of seven classes of chemicals implicated in initiating cases of MCS, all of which can act to elevate NMDA activity and produce toxic responses in the human body through such NMDA elevation. It provides mechanisms for the generation of symptoms in MCS patients, both symptoms that are shared with such related illnesses as CFS, FM and PTSD and also chemical sensitivity symptoms that are viewed as being specific for MCS. It is supported by observations implicating excessive NMDA activity, excessive NO levels and oxidative stress, neural sensitization, elevated TRP receptor activity, elevated ONOO$^-$ levels and elevated levels of intracellular calcium in people afflicted with MCS, in animal models or both. While there has been little in the way of published studies on therapy for MCS, clinical trial data on the related illnesses CFS and FM provide support for the inference that such aspects as excessive oxidative stress, NO, NMDA activity, mitochondrial dysfunction and possibly inflammation and BH4 depletion have important causal roles in the generation of this group of illnesses. We have some clinical observations suggesting that complex protocols designed to normalize these several parameters can produce substantial rapid improvement in many MCS patients also avoiding chemical exposure, even among patients who have been ill for decades.

Having said that, there are many aspects of this proposed MCS mechanism that need much study. That is not surprising, given the extraordinarily low level of funding that has been available for such studies. Pall (2002) estimated that although MCS has roughly the same prevalence as does diabetes in the USA, the funding available for research on MCS has been approximately 1/1000th of the funding for diabetes. This low level of funding is despite the fact that what little data we have on comorbid diseases for MCS (Baldwin and Bell, 1998; Bell *et al*., 1995; Baldwin *et al*., 1997; Baldwin *et al*., 1999) and the substantial impact on employment of MCS patients both suggest that the morbidity associated with MCS and its associated comorbid diseases may be comparable to that found as a consequence of diabetes.

The five areas that are in most need of further study, in my judgement, are:

1. Animal model studies testing various aspects of this mechanism that have never been adequately tested.
2. Studies to establish one or more low-level chemical exposure tests as specific biomarker tests for MCS.
3. Clinical trial studies on agents and groups of agents aimed at down-regulating various aspects of the proposed mechanism as potential therapeutic protocols for the treatment of MCS patients.
4. Studies of some of these same agents in placebo-controlled studies to determine if they can lower responses to low-level chemical exposure in MCS patients. These might be done in conjunction with the specific biomarker tests in item 2.
5. Use of bioassays described above to ascertain likely chemicals in the air of mould-infested 'sick buildings' to determine what mycotoxins are involved and what moulds produce them under what culture conditions. Promising methods have been developed for such bioassays (Hirvonen *et al*., 1997a; Hirvonen *et al*., 1997b; Ruotsalainen *et al*., 1995), but we are still plagued by many examples of such 'sick buildings' due in part to our stunning ignorance about the mycotoxins involved and their mechanisms of action.

NOTES

[a.] The most important physiological agonist for the NMDA receptors is L-glutamate; NMDA stands for *N*-methyl-D-aspartate, a nonphysiological agonist that is specific for these receptors, not acting as an agonist for other, non-NMDA glutamate receptors.

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Queries in Chapter XX

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Abstract: Cases of multiple chemical sensitivity (MCS) are initiated by exposure to organic solvents and three classes of pesticides. Each of these can act indirectly to increase NMDA activity and the toxic effects of members of each of these classes can be lowered by using NMDA antagonists. Other chemicals, mercury, H_2S and CO exposure may also initiate cases of MCS and have toxic responses mediated through increased NMDA activity. Thus each of these types of chemicals appears to act as a toxicant through increased NMDA activity. Six additional types of evidence suggest roles for elevated NMDA activity in MCS, suggesting that this response is involved, not only in MCS case initiation, but also in response to low-level chemicals in those who are already sensitive. The inference that chemicals act as toxicants in MCS is confirmed by three genetic studies showing that five genes that encode enzymes that metabolize these chemicals act to determine MCS susceptibility.

The chronic nature of MCS is thought to be produced by a local biochemical vicious cycle mechanism, the $NO/ONOO^-$ cycle, which is initiated by nitric oxide acting through its oxidant product peroxynitrite, which are both produced in MCS in response to excessive NMDA activity. Cycle elements, including NMDA activity, intracellular calcium, nitric oxide and peroxynitrite are thought to interact with other mechanisms, including neural sensitization in the brain and neurogenic inflammation in peripheral tissues to produce the high-level chemical sensitivity that is the hallmark of MCS. This complex model of MCS is supported by the following types of observations: MCS correlates in the chronic phase of illness, extensive animal model studies implicating almost all $NO/ONOO^-$ cycle elements, clinical trial data in the related illnesses chronic fatigue syndrome and fibromyalgia, and a variety of objectively measurable responses to low-level chemical exposure in MCS patients, responses that should be further studied as possible specific biomarker tests for MCS. While plausible mechanisms are proposed for the generation of both shared and specific symptoms and signs in MCS, there are little data on whether these mechanisms are actually involved in generating these symptoms and signs in MCS. Previous claims that MCS is produced by some sort of psychogenic mechanism have multiple flaws and are inconsistent with the various types of evidence discussed above. Several areas of research are discussed in which the author argues that research will be richly rewarded.

Keywords: *N*-methyl-D-aspartate (NMDA) receptors; oxidative stress; nitrosative stress; chronic inflammatory biochemistry; local vicious cycle mechanism; prevalence of multiple chemical sensitivity; sick building syndrome; moulds and mycotoxins; multiple chemical sensitivity case definitions

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