

MULTIPLE CHEMICAL SENSITIVITIES

I. General information on multiple chemical sensitivities

Multiple chemical sensitivities is an acquired condition in which the sufferer becomes sensitised or abnormally reactive to volatile chemicals following prolonged, recurrent or high dose exposure to volatile chemicals. The most distinctive symptom is “cacosmia”, or a heightened sensitivity and lowered threshold to odours that most of the population find inoffensive or would not notice.

Multiple chemical sensitivities is a condition that primarily affects the nervous system, particularly the brain, and most often has characteristic symptoms, including

- decreased short-term memory,
- poor concentration,
- weakness,
- fatigue,
- dizziness, and
- altered emotional states (emotional lability, often oscillating between anxiety and depression).

Recent published studies demonstrate alterations of SPECT brain scans, central evoked responses (especially visual and auditory), and altered autonomic nervous system function. The mechanisms of such damage remain unclear at present, but direct neurotoxicity is regarded as the most likely cause. There is no current evidence that the condition is reversible, and MCS appears to represent a form of subtle toxic brain damage with the potential for lifelong disability.

The sufferer’s history and clinical state should meet the criteria laid down by Cullen, that multiple chemical sensitivities is “...an acquired disorder characterised by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with the symptoms.” (Cullen MR. *The worker with multiple chemical hypersensitivities: An overview.* Occup Med 1987;2: 655-661)

This and subsequent publications suggest that the critical defining features of multiple chemical sensitivities are that

- it is an acquired disorder;
- sufferers have recurring symptoms;
- symptoms involve more than one organ system;
- reactions and exacerbations are triggered by many chemically diverse substances;
- reactions persist after separation of the person from the original causative agent(s)
- reactions and exacerbations occur at very low exposure

Specific tests such as Auditory Evoked Response Potential (AERP) testing and SPECT brain have shown significant changes in people suffering multiple chemical sensitivities, and these changes are consistent with neurotoxic brain damage. Minimising of exposure is the only proven way of reducing the disability experienced, as there is no form of treatment proven to be effective.

The degree of disability suffered by those suffering is very high, and there is currently no clear evidence as to whether the damage to the nervous system is permanent. Based on my clinical experience with over 500 sufferers in the past nine years, is that complete recovery is rare, and that the condition is associated with a variable degree of permanent neurological impairment, or brain damage, in adults. Most sufferers are able to adapt to the condition, varying their lifestyles to reduce the impact of their chemical sensitivity on their health.

It is more difficult to make an informed judgement regarding recovery in children. Full recovery would be more likely in pre-pubertal children, assuming that they have minimal ongoing exposure, because of the ability of neurons (brain cells) to regenerate and form new links during those years. Whether this does happen is an entirely different, and at present unanswered, question.

Although described and defined by Cullen in 1987, acceptance of multiple chemical sensitivities as a distinct clinical entity (disease) has been slow in occurring. The fact that the dosage for such damage is so low, and apparently 'neurotic' symptoms are maintained many years after exposure, has led many people to dismiss it as a psychological complaint, or a psychiatric disease. As increasing evidence of neuro-biochemical and neuropathological changes accrue, this view is currently changing among serious researchers.

Of the articles and letters in the peer reviewed medical literature from 1993 to 1996, the majority now support the view of multiple chemical sensitivities as a distinct clinical entity deserving of further research. Of the original articles (as opposed to letters, opinions and editorials), about two thirds identify non-psychiatric causes and contributions as being of major importance in the development of multiple chemical sensitivities, while under one third attribute the disorder to psychiatric or psychological causes. All note the neuropsychological abnormalities in sufferers. This is a significant reversal of the weight of medical opinion presented in the peer reviewed medical literature in the five years prior to 1993.

In my opinion, it is now correct to say that the majority of the medical literature on the subject supports the existence of multiple chemical sensitivities as a distinct disease, identifies both specific and non-specific organ pathology, and implicates low level exposure as a significant factor in causation and going symptom generation.

In Australia in 1997, however, the majority of physicians are unaware of the change in scientific perspective on this condition in the past five years. Others, who have previously made public their incredulity about the existence of the syndrome, appear to have understandable difficulties in changing their viewpoint based on the recent available data.

While the disease is now generally well accepted as a clinical entity, however, the mechanisms of damage and therapeutic approaches which may be of benefit to sufferers are far from elucidated. This is true for many diseases, however, including Multiple Sclerosis, most cancers, and sudden infant death, to name only a few.

II. References and abstracts on multiple chemical sensitivities

Medline 1991 - 1997

1. *Multiple chemical sensitivities and neurotoxic responses*

Lohmann K Prohl A Schwarz E

[Multiple chemical sensitivity disorder in patients with neurotoxic illnesses]

Vielfache Chemikalienunverträglichkeit (Multiple Chemical Sensitivity Disorder) bei Patienten mit neurotoxischen Gesundheitsstörungen.

In: Gesundheitswesen (1996 Jun) 58(6):322-31 (Published in German)

The data of 466 subjects suffering from neurologic disorders which are suggested to be caused by neurotoxic agents in their environment retrospectively was evaluated and documented. Among these cases there were 151 subjects with symptoms of Multiple Chemical Sensitivity Disorder (MCSD). The relationship between the neurological health impairments and neurotoxic agents in the environment of these patients was characterised using five different categories (probable = A, possible = B, uncertain = C, unclarified = D, not probable = E). From the 466 patients 320 subjects (69%) could be assigned to the categories A and B, respectively. Within these 320 cases with chronic neurotoxic health impairments 136 subjects (79 females and 57 males) showed signs of MCSD. Age and gender of cases as well as duration and character of exposure to neurotoxic substances retrospectively were assessed from the explicit files of the patients, which had been made anonymous for this purpose. Frequency of characteristic symptoms of neurotoxicity were analysed. Results are given for patients with neurotoxic health impairments with MCSD (n = 136) and without MCSD (n = 184). Neurotoxic substances which were used as indoor wood preservatives (mainly Pentachlorophenol and/or Lindane) were found to be the causative agents in 63% of the cases with neurotoxic health impairments and MCSD. Other important neurotoxic substances to which the patients were mainly exposed were organic solvents (25%), formaldehyde (15%), dental materials (15%), pyrethroids (13%), and other biocides (19%) (multiple exposures were possible). The time of exposure was calculated as being > or = 10 years for 55% of the patients with MCSD and for 50% of the group with neurotoxic health impairments but without MCSD. Out of the 184 cases with neurotoxic health impairments but without MCSD there were 22%, and out of the 136 cases with MCSD there were 39% who showed all symptoms of chronic fatigue syndrome. 53% of the cases with MCSD had an allergic disposition compared to only 20% of the cases without MCSD. This work is not a controlled epidemiological study but a retrospective documentation and evaluation of data related to environmental medicine. With the present documentation in this purely descriptive manner the proof of a causal relationship was not possible or intended. But because corresponding epidemiological studies are lacking, this documentation can give important information on characteristic features of Multiple Chemical Sensitivity Disorder and chronic neurotoxic health impairments. Such information is essential for planning and carrying out epidemiological studies urgently needed in this field.

2. *MCS related to indoor solvent exposure - means of minimising incidence of MCS*

Lax MB Henneberger PK

Patients with multiple chemical sensitivities in an occupational health clinic: presentation & follow-up.

In: Arch Environ Health (1995 Nov-Dec) 50(6):425-31

Thirty-five people with work-related Multiple Chemical Sensitivities were studied to learn about the onset and progression of illness. The subjects were selected from patients at an occupational health clinic. Individuals were identified as subjects if they fulfilled a seven-point case definition for Multiple Chemical Sensitivities and if onset of symptoms was related to workplace exposures. Three occupational exposures to solvents, poor indoor-air quality, and remodeling were associated with onset of Multiple Chemical Sensitivities in 63% of the subjects. Symptoms indicative of a nervous-system disorder topped the list of the most frequently reported symptoms. Commonalities in exposures and symptoms suggest that Multiple Chemical Sensitivities represents a distinct diagnostic category. Even with an incomplete understanding of etiology, it may be possible to limit the onset of work-related Multiple Chemical Sensitivities.

3. *Describes need for improved biomarkers in multiple chemical sensitivities*

Cullen MR Redlich CA

Significance of individual sensitivity to chemicals: elucidation of host susceptibility by use of biomarkers in environmental health research.

In: Clin Chem (1995 Dec) 41(12 Pt 2):1809-13

Biomarker research has become the predominant theme for study of human dose-host-response relations to environmental chemicals. Increasing interest has been focused on identifying markers for host susceptibility, with mixed results. Efforts to identify markers for host variability in carcinogenic risk, on the basis of theoretical knowledge of carcinogen metabolism, have been disappointing. New work in the area of acquired risk modifiers, such as nutritional status, is theoretically attractive, but results have been limited. Impressive achievements have been made in the area of immunological variability, which may elucidate the molecular basis of as well as provide practical biomarkers for several diseases. The problem of multiple chemical sensitivities, on the other hand, has proved refractory to biomarker research, reflecting inadequate knowledge of the mechanism and inappropriate application of biomarker methods.

4. *Suggests a major change in toxicological viewpoint is needed for understanding MCS*

Bronstein AC

Multiple chemical sensitivities--new paradigm needed.

In: J Toxicol Clin Toxicol (1995) 33(2):93-4

The current principles of toxicology, immunology and allergy do not provide a coherent explanation of a chemical sensitivity lacking reproducible and measurable physiologic or biochemical changes. A new paradigm is needed as a scientific model for multiple chemical sensitivities.

5. *Limbic system alteration in multiple chemical sensitivities patients*

Bell IR Miller CS Schwartz GE

An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders.

In: Biol Psychiatry (1992 Aug 1) 32(3):218-42

This paper reviews the clinical and experimental literature on patients with multiple adverse responses to chemicals (Multiple Chemical Sensitivity Syndrome-MCS) and develops a model for MCS based on olfactory-limbic system dysfunction that overlaps in part with Post's kindling model for affective disorders. MCS encompasses a broad range of chronic polysymptomatic conditions and complaints whose triggers are reported to include low levels of common indoor and outdoor environmental chemicals, such as pesticides and solvents. Other investigators have found evidence of increased prevalence of depression, anxiety, and somatization disorders in MCS patients and have concluded that their psychiatric conditions account for the clinical picture. However, none of these studies has presented any data on the effects of chemicals on symptoms or on objective measures of nervous system function. Synthesis of the MCS literature with large bodies of research in neurotoxicology, occupational medicine, and biological psychiatry, suggests that the phenomenology of MCS patients overlaps that of affective spectrum disorders and that both involve dysfunction of the limbic pathways. Animal studies demonstrate that intermittent repeated low level environmental chemical exposures, including pesticides, cause limbic kindling. Kindling (full or partial) is one central nervous system mechanism that could amplify reactivity to low levels of inhaled and ingested chemicals and initiate persistent affective, cognitive, and somatic symptomatology in both occupational and nonoccupational settings. As in animal studies, inescapable and novel stressors could cross-sensitize with chemical exposures in some individuals to generate adverse responses on a neurochemical basis. The olfactory-limbic model raises testable neurobiological hypotheses that could increase understanding of the multifactorial etiology of MCS and of certain overlapping affective spectrum disorders.

6. *Increased limbic (brain) dysfunction in chemical versus other sensory sensitivity*

Bell IR Hardin EE Baldwin CM Schwartz GE

Increased limbic system symptomatology and sensitizability of young adults with chemical and noise sensitivities.

In: *Environ Res* (1995 Aug) 70(2):84-97

We previously hypothesized that individual differences in (a) limbic system reactivity and (b) central nervous system sensitizability underlie vulnerability to environmental stimuli, not only in the controversial clinical condition multiple chemical sensitivity (MCS), but also in the general population. Earlier research has shown overlaps in the characteristics of persons who report noise and air pollutant sensitivities. This study assessed questionnaire responses of 897 young adult college students who reported high versus low frequency of illness from several environmental chemical odors and concomitantly high versus low sensitivity to environmental noise. Subjects who reported increased rates of illness from chemical odors with or without noise sensitivity scored significantly higher ($P < 0.0001$) on a measure of limbic system symptomatology derived from ictal sensory, somatic, mnemonic, and behavioral manifestations of temporal lobe epilepsy. The group rating high both for illness from chemicals and for noise sensitivity had characteristics predictive of heightened sensitizability from the animal research on time-dependent sensitization (progressive response amplification to repeated, intermittent stimuli over time): i.e., higher female to male ratio (gender risk factor), increased rates of drug abuse problems in blood relatives (genetic risk factor), trait shyness (hyperreactivity to novelty), and increased carbohydrate craving. Despite the increased family histories of drug abuse and levels of personal anxiety and depression, the chemical- and noise-sensitive group reported the lowest rates of current smoking or personal drug abuse problems and the highest frequency of illness from drinking a small amount of alcohol. Taken together, the findings suggest that limbic system dysfunction associates more with chemical than with noise sensitivity; that individuals with both chemical and noise sensitivity may be the most sensitizable subset of the population for prospective studies, and that, in their substance use patterns, young adults with both chemical and noise sensitivity are more similar to MCS patients than are their peers with chemical or noise sensitivity alone.

7. *Altered sensitivity of GABA receptor as a basis for increased neurological responses in MCS*

Corrigan FM MacDonald S Brown A Armstrong K Armstrong EM

Neurasthenic fatigue, chemical sensitivity and GABA_A receptor toxins.

In: *Med Hypotheses* (1994 Oct) 43(4):195-200

Following observation of fatigue syndromes in people who have been occupationally exposed to pesticides and insecticides which exert their toxicity through the GABA_A receptor, we have formulated the hypothesis that fatigue syndromes in general may be secondary to altered sensitivity of the GABA_A receptor. We discuss the possible involvement of organochlorine compounds which are widespread in the environment. Organophosphate compounds may have similar toxic effects through damaged cholinergic input to the dentate gyrus of the hippocampus where cholinergic and GABA_Aergic transmission are closely linked.

8. *Failure of classic toxicology to identify and characterize MCS and low level neurotoxic responses*

Weiss B

Low-level chemical sensitivity: a perspective from behavioral toxicology.

In: *Toxicol Ind Health* (1994 Jul-Oct) 10(4-5):605-17

Low-level chemical sensitivity is hardly a new issue in environmental toxicology. It is, in fact, the focus of risk assessment. The risk assessment process is designed explicitly to estimate the health threats posed by low exposure levels, typically by extrapolating from high experimental or environmental levels. The conventional risk assessment structure, however, was designed primarily around cancer. It is only awkwardly applicable to neurobehavioral toxicants because of the multiplicity of endpoints that have to be considered in evaluating neurotoxicity. At the same time, neurotoxic risk assessment maintains certain advantages over cancer risk assessment because of diminished uncertainties over dose extrapolation. It does not have to depart as far from the range of observable data. The main problem with extending the risk assessment model to issues such as Multiple Chemical Sensitivity (MCS) and Sick Building Syndrome (SBS) is the absence of a specific chemical whose concentration can be measured and then manipulated. A prototypical agent, however, such as a volatile organic solvent, might be selected and studied. Beyond the choice of agent, however, is the question of which behavioral criteria are likely to yield the most useful information. Although neuropsychological test batteries provide one source of data, they typically are administered in a setting other than the one allegedly provoking the syndrome. A different approach invokes what might be called a miniature work situation. Here, a test subject is evaluated in a setting that emphasizes sustained performance testing in the presence of target chemicals. Experimental design is another factor to be considered. Two features are especially critical. The most sensitive design, at least for the current stage of knowledge, would probably emphasize consistency of response, and would choose as subjects individuals who claim to be afflicted with low-level sensitivity. Consistency in a single individual may be more informative than significance tests in a large sample. In addition, consistency as a criterion helps overcome the problem that, in any such sample, only a minor proportion of the subjects may truly exhibit such sensitivity. At a later stage, a broader range of subjects might be targeted. Research on behavioral disorders evoked by food additives illustrates the importance of such questions. It also demonstrates that the methods currently used to assess the potential toxicity of many substances, including food additives, typically ignore subtle, and often sensitive, neurobehavioral measures.

9. *Changes in GABA vs NMDA neurological activity as basis for MCS-like neuro effects*

Adamec R

Modelling anxiety disorders following chemical exposures.

In: *Toxicol Ind Health* (1994 Jul-Oct) 10(4-5):391-420

The effects of kindling and inverse benzodiazepine receptor agonist beta-carbolines on animal models of anxiety are briefly reviewed in relation to affective disorder associated with chemical exposure. Recent experimental results are described. In the present study, cats were given the inverse benzodiazepine receptor agonist, FG-7142, a powerful anxiogenic compound in humans and animals. Neural transmission in pathways involved in defensive behavior in the cat was monitored using evoked potential techniques. Change in these pathways was related to behavioral changes induced by the drug. It was found that a single dose of FG-7142 lastingly increased defensive response to rodents for at least 40 days after drug administration. Behavioral change was specific to defensive response, since approach- attack behavior remained unchanged, replicating previous studies. The benzodiazepine receptor antagonist, Flumazenil, reversed the increase in defensiveness in a drug-dependent manner, replicating previous findings. Increased defensiveness was paralleled by a delayed onset potentiation of neural transmission between the amygdala and the medial hypothalamus of the left hemisphere. Potentiation in the left hemisphere was transient, decaying between 6 and 12 days after the drug. There was a longer lasting potentiation (LTP) of activity evoked in the left and right amygdalo-periaqueductal gray pathways and in the right amygdalo-medial hypothalamic pathway. Potentiation in these pathways appeared at the time of behavioral change. Potentiation of the right amygdalo-periaqueductal gray and right amygdalo-medial hypothalamic pathways persisted until the end of the experiment. In contrast, potentiation of the left amygdalo-periaqueductal gray pathway faded by 40 days after the drug. Flumazenil decreased potentiation only in the right amygdalo-periaqueductal gray pathway. These data strongly suggest that lasting affective change is mediated by lasting changes in particular efferents of the amygdala of the right hemisphere. Behavioral and physiological effects of FG-7142 were blocked by the N-methyl-D- Aspartate (NMDA) receptor blocker, AP7. The data suggest that failure of neural inhibition induced by FG-7142 engages NMDA receptor processes to produce lasting potentiation of transmission in neural circuits that mediate defensive response with behavioral consequences. Since FG-7142 interferes with GABA mediated neural inhibition and is proconvulsant, its action might mimic the action of other environmental chemicals with similar properties, such as chlorinated hydrocarbon insecticides. The relationship of the present data to the literature on the neural and behavioral effects of insecticide exposure is discussed. The significance of these findings for multiple chemical sensitivity disorder is also briefly discussed.

10. *Simple model of chemical sensitisation derived from animal observational studies*

Antelman SM

Time-dependent sensitization in animals: a possible model of multiple chemical sensitivity in humans.

In: *Toxicol Ind Health* (1994 Jul-Oct) 10(4-5):335-42

It often happens in science that clues to the nature of a problem under study come from a completely different, seemingly unrelated, line of investigation. This may be the case with MCS and Time- Dependent Sensitization (TDS), a phenomenon we discovered in rats in the late 1970s and later named. TDS refers to the ability of mild stressors--whether pharmacological or environmental--to induce physiological and behavioral effects which then progress, i.e., get stronger, entirely as a function of the passage of time since stressor presentation. This strengthening is revealed when the organism is later exposed to either the original or another stressor. The characteristics of TDS bear a remarkable resemblance to the features of MCS and that similarity is the subject of this manuscript.

11. *Limbic system as target organ within the brain for explaining symptoms of MCS*

Miller CS

Possible models for multiple chemical sensitivity: conceptual issues and role of the limbic system.

In: *Toxicol Ind Health* (1992 Jul-Aug) 8(4):181-202

Conceivably, chemicals contacting olfactory nerve projections in the nose could either be transported into or relay electrical signals to the limbic region, leading to a vast array of symptoms. Likewise, thought processes and mood states may trigger or interrupt pre-existing limbic activity. At present, however, no evidence suggests that limbic activity triggered by environmental exposures can be entirely overcome by psychologic interventions. One important ramification of a limbic hypothesis, if true, is that no convenient biologic marker for multiple chemical sensitivity may exist at the present time. Ten years from now, we may finally confirm the existence of multiple chemical sensitivities (by careful, blinded challenges) but still have no single mechanism to explain it; that is, after all avenues of biochemical and immunologic inquiry have been exhausted, no single cause or marker for this disorder may be apparent. The theory that adaptation plays a role in MCS is based on the observed responses of patients in a deadadapted state who have been housed in an environmental unit. Although adaptation is only an observation at this time, not a mechanism, biologic limits might regulate how much an organism can adapt. Such limits could be highly individual and vary by orders of magnitude. Certainly adaptation occurs at all levels of biologic systems, from enzyme systems to cells, tissues, organs, and even behavior (Fregly, 1969). Theoretically, a major insult or the accumulation of lower-level injuries within these systems could lead to a kind of "overload" or "saturation" effect with respect to adaptive capacity. This might cause an individual to have environmental responses, which, instead of being flexible and fluid, would become fragile and overly responsive. Many MCS patients report that years, and in some cases decades, after the onset of their problems, they have recovered only a portion of their former energies and tolerance for their environment. Their descriptions seem to suggest the loss of an intangible capacity to adapt, parts of which may be temporary and recoverable and other parts of which may not. Perhaps our patients have been telling us the diagnosis.

12. *Quality review paper on issues surrounding multiple chemical sensitivities*

Miller CS

Chemical sensitivity: symptom, syndrome or mechanism for disease?

In: *Toxicology* (1996 Jul 17) 111(1-3):69-86

Several different meanings have been attached to the term "chemical sensitivity" by those who use it. Feeling ill from odors is a symptom reported by approximately one-third of the population. The syndrome of chemical sensitivity, frequently called "Multiple Chemical Sensitivity" or "MCS" has been the subject of three federally-sponsored workshops; at least five different case definitions for research on MCS have been proposed. In contrast, the hypothesis that chemical sensitivity may be a mechanism for disease posits that a broad spectrum of "recognized" chronic illnesses, ranging from asthma and migraine to depression and chronic fatigue, may be the consequence of environmental chemical exposures. According to this theory, a two-step process occurs: (1) an initial salient exposure event(s) (for example, a one-time, intermittent, or continuous exposure to pesticides, solvents, or air contaminants in a sick building) interacts with a susceptible individual, causing loss of tolerance for everyday, low level chemical inhalants (car exhaust, fragrances, cleaning agents), as well as for foods, drugs, alcohol, and caffeine; (2) thereafter, such common, formerly well-tolerated substances trigger symptoms, thus perpetuating illness. "Masking" (acclimatization, apposition, and addiction) may hide these exposure-symptom relationships, thus obfuscating the environmental etiology of the illness. Accumulating clinical observations lend credence to a view of chemical sensitivity as an emerging theory of disease causation and underscore the need for its testing in a rational, scientific manner. While chemical sensitivity may be the consequence of chemical exposure, the term "toxicant-induced loss of tolerance" more fully describes the two-step process under scrutiny.

13. *Hypothesis of alteration of sulfa-dependent detoxication pathways in humans as basis of MCS*

McFadden SA

Phenotypic variation in xenobiotic metabolism and adverse environmental response: focus on sulfur-dependent detoxification pathways.

In: *Toxicology* (1996 Jul 17) 111(1-3):43-65

Proper bodily response to environmental toxicants presumably requires proper function of the xenobiotic (foreign chemical) detoxification pathways. Links between phenotypic variations in xenobiotic metabolism and adverse environmental response have long been sought. Metabolism of the drug S-carboxymethyl-L-cysteine (SCMC) is polymorphous in the population, having a bimodal distribution of metabolites, 2.5% of the general population are thought to be nonmetabolizers. The researchers developing this data feel this implies a polymorphism in sulfoxidation of the amino acid cysteine to sulfate. While this interpretation is somewhat controversial, these metabolic differences reflected may have significant effects. Additionally, a significant number of individuals with environmental intolerance or chronic disease have impaired sulfation of phenolic xenobiotics. This impairment is demonstrated with the probe drug acetaminophen and is presumably due to starvation of the sulfotransferases for sulfate substrate. Reduced metabolism of SCMC has been found with increased frequency in individuals with several degenerative neurological and immunological conditions and drug intolerances, including Alzheimer's disease, Parkinson's disease, motor neuron disease, rheumatoid arthritis, and delayed food sensitivity. Impaired sulfation has been found in many of these conditions, and preliminary data suggests that it may be important in multiple chemical sensitivities and diet responsive autism. In addition, impaired sulfation may be relevant to intolerance of phenol, tyramine, and phenylic food constituents, and it may be a factor in the success of the Feingold diet. These studies indicate the need for the development of genetic and functional tests of xenobiotic metabolism as tools for further research in epidemiology and risk assessment.

14. *Animal model of sensitisation of central nervous system, involving cross sensitisation*

Sorg BA Willis JR Nowatka TC Ulibarri C See RE Westberg HH

Proposed animal neurosensitization model for multiple chemical sensitivity in studies with formalin.

In: *Toxicology* (1996 Jul 17) 111(1-3):135-45

A potentially promising line of animal research relevant to multiple chemical sensitivity (MCS) is that of sensitization in the central nervous system (CNS), particularly limbic pathways in the brain. Sensitization is the progressive and enduring enhancement in behavioral and neurochemical responses that occurs after repeated exposure to psychostimulants or environmental stressors. Since the onset and progression of sensitization has many parallels with that of MCS, it has been proposed that MCS may be initiated through a mechanism similar to the sensitization of CNS components occurring in the rodent. To test this hypothesis, female Sprague-Dawley rats were exposed to formalin vapors (FORM, 11 ppm) or water vapor (control) 1 h/day for 7 days. The next day, saline injection was given followed by a cocaine injection (15 mg/kg, i.p.) 24 h later, and locomotor activity was monitored. Animals pretreated with repeated FORM inhalation demonstrated a significantly enhanced locomotor response to cocaine compared to controls, an indicator that specific limbic pathways may have been sensitized. At 4 weeks of withdrawal from FORM exposure, a subset of animals remained sensitized to a cocaine challenge. No differences were found between groups after a saline injection. In a second experiment, animals were screened prior to FORM or water exposure for their response to a novel situation, a measure believed to reflect an animal's general responsiveness to stimuli. Rats were divided into high responders (HR) or low responders (LR), based on their locomotion in a novel cage. Results from three behavioral tests demonstrated that HR and LR were differentially affected by exposure to FORM. In a passive avoidance test, HR and LR appeared to be different in their distribution of responses, while HR and LR responses in the FORM group were nearly identical. On the elevated plus maze test of anxiety, HR spent more time on the open arms than LR in both treatment groups, with significant differences between HR and LR in the FORM, but not water, treated group. On a hot plate test to measure nociceptive levels, no differences occurred between HR and LR in the control group, whereas nociception of LR tended toward an increase compared to HR in the FORM-exposed group. Results from the second experiment suggest that the effects of FORM exposure may be obscured by examining behavior in a heterogeneous population (HR and LR). This approach using animal models may help define neural substrates that mediate the amplification of responses of a subpopulation of individuals to chemicals in the environment.

15. *An animal model of enzyme defects as a mechanism of amplification of neurotoxic response*

Overstreet DH Miller CS Janowsky DS Russell RW

Potential animal model of multiple chemical sensitivity with cholinergic supersensitivity.

In: *Toxicology* (1996 Jul 17) 111(1-3):119-34

Multiple Chemical Sensitivity (MCS) is a clinical phenomenon in which individuals, after acute or intermittent exposure to one or more chemicals, commonly organophosphate pesticides (OPs), become overly sensitive to a wide variety of chemically-unrelated compounds, which can include ethanol, caffeine and other psychotropic drugs. The Flinders Sensitive Line (FSL) rats were selectively bred to be more sensitive to the OP diisopropylfluorophosphate (DFP) compared to their control counterparts, the Flinders Resistant Line (FRL) rats. The present paper will summarize evidence which indicates that the FSL rats exhibit certain similarities to individuals with MCS. In addition to their greater sensitivity to DFP, the FSL rats are more sensitive to nicotine and the muscarinic agonists arecoline and oxotremorine, suggesting that the number of cholinergic receptors may be increased, a conclusion now supported by biochemical evidence. The FSL rats have also been found to exhibit enhanced responses to a variety of other drugs, including the serotonin agonists m-chlorophenylpiperazine and 8-OH-DPAT, the dopamine antagonist raclopride, the benzodiazepine diazepam, and ethanol. MCS patients report enhanced responses to many of these drugs, indicating some parallels between FSL rats and MCS patients. The FSL rats also exhibit reduced activity and appetite and increased REM sleep relative to their FRL controls. Because these behavioral features and the enhanced cholinergic responses are also observed in human depressives, the FSL rats have been proposed as a genetic animal model of depression. It has also been reported that MCS patients have a greater incidence of depression, both before and after onset of their chemical sensitivities, so cholinergic supersensitivity may be a state predisposing individuals to depressive disorders and/or MCS. Further exploration of the commonalities and differences between MCS patients, human depressives, and FSL rats will help to elucidate the mechanisms underlying MCS and could lead to diagnostic approaches and treatments beneficial to MCS patients.

16. *Hypothetical neural mechanisms proposed for multiple chemical sensitivities.*

Bell IR

Clinically relevant EEG studies and psychophysiological findings: possible neural mechanisms for multiple chemical sensitivity.

In: *Toxicology* (1996 Jul 17) 111(1-3):101-17

This paper addresses the evidence for the face, construct, and criterion-related validity of the olfactory-limbic/neural sensitization model for multiple chemical sensitivity (MCS). MCS is a poorly-understood, controversial condition in which low levels of environmental chemicals are reported to trigger disabling levels of illness in certain individuals. Neural sensitization processes could generate an endogenous amplification of responsivity to exogenous substances, thereby providing a plausible explanation for the apparent lack of a classical toxicological dose-response relationship in MCS. Convergent data from both survey and psychophysiological studies of MCS patients and of persons from the community without MCS, but who report elevated frequency of illness from chemical odors (cacosmics), support the involvement of the limbic system and the sensitizability of cacosmics, as predicted by the model. Recent studies show that cacosmics do sensitize their heart rate, blood pressure, and plasma beta-endorphin responses to repeated exposures to a novel laboratory procedure involving dietary manipulations over time. Cacosmia may represent a pathological form of neural plasticity. Taken together, the model and the available evidence suggest the need for more intensive investigation of MCS from the standpoint of possible neurobiological mechanisms affecting cognitive, emotional, and somatic functions.