Engaging with Multiple Chemical Sensitivity (MCS)- London 2003

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Introduction

Multiple chemical sensitivity, MCS, was first officially recognised in Germany and is now included in its edition of the WHO's International Classification of Diseases, ICD-10, under the code T 78.4. Interestingly, this code is for "allergy, otherwise not specified".

The recent report "Allergy the Unmet Need", Royal College of Physicians, June 2003, records the huge increase in allergy in the UK with 1 person in 3 suffering some form of allergy, a total of 18 million people. Of these 18 million some 3 million suffer from severe allergies which can be life-threatening and require emergency treatment.

The release of the Royal College of Physician's report coincided with the publication of, another very large report, the Royal Commission on Environmental Pollution, 24th Report, "Chemicals in Products: safeguarding the environment and human health." This report identifies the need for a proper understanding of the health effects of novel chemicals widely used in society and distributed ubiquitously in the environment. Some 30,000 chemicals with little or no toxicology now need to be assessed, an enormous undertaking.

I do not think these reports are unrelated. The rise of allergy, chemical toxicity and MCS are consistent with the disturbing data in these reports. The Germans have surely embarked on the right course. If we are to engage with MCS as a feature of health care in our modern societies and even more so in the developing economies of what is sometimes referred to as the third world then we need new ways of diagnosing and treating MCS and related illnesses. Otherwise there will be a legacy of ill-health added to the burden of third world countries and the poor in all societies.

In the USA official recognition has come in the form of reports from the Department of Justice, the Department of Housing and Urban Development, and the Department of Education, which accept MCS as a legitimate condition for their purposes, CFIDS Chronicle, 1997. Medical resistance to MCS has begun to evaporate among the American College of Physicians. The American Medical Association and American Lung Association and Environmental Protection Agency state that, "Claimants should not be dismissed as psychogenic and a thorough workup is essential…." . large population surveys report from 16-33% of people being sensitive to every day chemicals.

A consensus report by 89 physicians, University of Illinois at Chicago, 2001, defines MCS as a chronic condition in which symptoms-

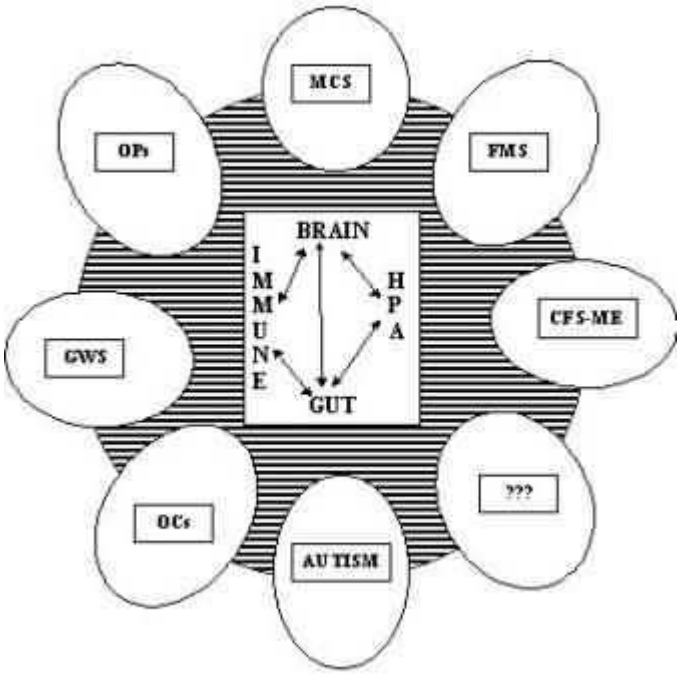
1. recur **reproducibly**
2. in response to **low levels of exposure**

3. in response to **multiple unrelated chemicals**
4. **improve or resolve** when incitants are **removed**
5. occur in **multiple organ systems**.

In the UK MCS has been resisted by the medical establishment generally, with some honorable exceptions. A major review by Gravelling et al, 1999, and a monograph from the British Society for Allergy, Environmental and Nutritional Medicine, 2001, provide substantial evidence for recognition of MCS an organic illness that can be diagnosed and treated effectively. A major textbook has appeared that provides a comprehensive understanding of MCS, Ashford and Miller, 1998.

The triggering event for MCS is often associated with exposure, usually at a high level, to a single chemical entity, or a commercial product formulated in a complex mixture which is frequently thought to be inert. There then develops widespread sensitivity to very low dose exposures to a wide variety of quite different chemicals. This poses a significant puzzle for clinicians, toxicologists, allergists, and medicinal chemists.

Our own work, Figure 1, identifies MCS is one of several recognised overlapping syndromes, Merck 1999; Hooper, 2000, 2003; see also Donnay 1997, which share a common core of biochemical dysfunctions involving the gut, nervous, immune and endocrine systems.



??? many other syndromes can be added here. IBS (irritable bowel syndrome), Carbon monoxide poisoning, other pesticide poisoning eg pyrethroids; post polio syndrome, post viral fatigue syndrome.
Key: OCs = organochlorine pesticides; OPs = organophosphate pesticides; FMS = Fibromyalgia Syndrome; HPA = Hypothalamus-Pituitary-Adrenal axis

Figure 1. Overlapping syndromes sharing a common core of biochemical deficits.

It is interesting to note that many Gulf War Veterans, Proctor, 2000; Wessely et al, 20001, OP and pesticide poisoned, Richardson, 2001, and ME-CFS, fibromyalgia, Donnay, 1997, patients report increased and disabling chemical sensitivities.

The symptoms shared by some overlapping syndromes are listed in Table 1. Although there is confusion and sometimes heated debate about the existence of CFIDS, the American description of ME-CFS, MCS, and OP poisoning there is no argument today about the neurological illness, MS, multiple sclerosis, or the immunological illness, HIV-AIDS. This data underlines the multiple system nature of these chronic illnesses.

Table 1. Common Symptoms shared by Seven different Chronic Illnesses

SYMPTOMS	OPs	GWS/I	MCS	FMS	CFIDS	MS	HIV/ AIDS
JOINT PAIN	+	+	+	**around joint area**	+	+	+
FATIGUE	+	+	+	+	+	+	+
HEADACHE	+	+	+	+	+	+	+
MEMORY PROBLEMS	+	+	+	+	+	+	+
SLEEP DISTURBED	+	+	+	+	+	**?? due to medicines**	+
SKIN PROBLEMS	+	+	+	+	+	**burning skin**	+
CONCENTR^{N} PROBLEMS	+	+	+	+	+	+	+
DEPRESSION	+	+	+	+	+	+	+
MUSCLE PAIN	+	+	+	+	+	+	+
DIZZINESS	+	+	+	+	+	+	+
G.I. - Irr. Bow.	+	+	+	+	+	+	+
PERIPH PARESTHES/ TINGLING	+	+	+	+	+	+	+
CHEM/ENVIR SENSITIVITY	+	+	+	+	+	**Reported**	_
EYE PROBLEMS	+	+	+	+	+	+	+
ANXIETY	+	+	+	+	+	+	+
TACHY&/OR CHEST PAIN	+	+	+	+	+	+	+
BREATHING PROBLEMS	+	+	+	**Reported**	+	+	+
LIGHT SENSITIVITY	+/-	+	+	**Reported**	+	+	_

OP = Organophosphate Poisoning; GWS/I = Gulf War Syndrome/Illness; MCS = Multiple Chemical Sensitivity; FMS = Fibromyalgia Syndrome; CFIDS = Chronic Fatigue Immune Dysregulation Syndrome = ME/CFS; MS = Multiple Sclerosis; HIV/AIDS = Acquired Immune Deficiency Syndrome.
+ Literature Reported ie. Anecdotal Adapted from Jackie Burkhead

Some agencies and doctors who insist on a psychiatric diagnosis have developed a terminology that confounds questions around MCS and the other overlapping syndromes. Usually the battery of standard tests provided to support clinical investigations yield little or no positive results leading to the false conclusion that there is "nothing wrong with the patient". Absence of evidence is taken as absence of evidence. No regard is given to the limited nature of the tests. The standard thyroid test(s) are particularly limited and recent work from Holland, European Laboratory of Nutrients, Baiser et al, 2000; Downing, 2000, has shown that an older test, involving a 24 hour urine sample, provides much more accurate and reliable tests. Nutritional deficits, particularly in selenium, have a major impact on the conversion of thyroxine (T4) to the much more active 3,5,3'-iodothyronine (T3).

New acronyms are invented to cloak medical ignorance of and unwillingness to engage with these chronic illnesses. Hence, SSIDC, signs and symptoms of ill-defined conditions, favoured by the War Pensions Agency, PUPS, persistent unexplained physical symptoms, MUPS, multiple unexplained physical symptoms, used by the Medical Assessment Panel of the Gulf Veterans Illness Unit, Lee et al, 2000, 2002, 2003.

CHEMICAL EXPOSURES

The Royal Commission report acknowledges the failure of self-regulation in the chemical industry and provides examples of lessons not learned from investigations in the past. These include the enormous problem of the organochlorine compounds first used as potent insecticides. The extensive worldwide impact of these compounds, first made public in Rachel Carson's ground breaking book, Silent Spring, 1962, should have alerted the chemical industry and related industries producing pharmaceuticals, herbicides, and pesticides, particularly DDT. But no! Now we have organochlorines ubiquitously distributed in human fat to such an extent that we are literally unfit to eat. Our flesh could not be sold in the market place- it would be banned as too heavily laden with toxic materials. The biological half-life of these compounds is of the order of 50 years, so once we are contaminated we are marked for life. The Inuits whose diet involves fatty meat from seals and fish carry one of the highest loads of organochlorines and breast feeding is limited by such contamination since the mother is feeding toxic compounds to her new born baby! The contamination of our food chain by organochlorines now limits the harvesting of essential omega-3 fatty acids from fatty fish, salmon, trout, mackerel, sardines and the like. In a cruel irony the recommended consumption of fish oils may prove toxic because of the level of contamination. When purchasing such oils it is important to know if organochlorine compounds are contained in them- ask and if no information is forthcoming then buy elsewhere. Despite this toxic compounds continued to be released.

The dioxin story is another salutary example. These organochlorines, 2,3,7,8-tetrachlorodibenzo[b,e][1,4]dioxin is the best known, are by-products from the

manufacture or incineration of chlorophenols used in agriculture and as antiseptics. The growing awareness of the toxicity of dioxins has lead to a progressive reduction in the exposure levels to these compounds, from nanogram, 10^{-9} g to picogram, 10^{-12} g quantities. This has not stopped the American military from contesting the excessive illnesses, varying from cancers to birth defects and the non-specific symptoms in Table 1, among Vietnam veterans resulting from the use of Agent Orange. Only after 20 years was it conceded that the use of Agent Orange a defoliant which contains only traces of dioxins as by-products of the manufacturing process, Bertell, 2000, Brown, 2001. The endocrine disrupting properties of dioxins released in an explosion of a manufacturing plant at Seveso in N. Italy were responsible for the change in the ratio of female to male human births which increased to 3:1 over the early birth cohorts. Birth ratios now appear to be normalising. But still there is a deficit of male children which is a world wide phenomenon and associated with chemical exposure of the mother whilst the child is *in utero*, Montague, 1998.

Heavy metal poisoning has also emerged as another major hazard worldwide. The recent large increase in autism in the USA, especially in California, is strongly associated the increasing dose of thiomersal, a mercury containing preservative that liberates ethylmercury in the body, and is widely used in vaccines, Geier and Geier, 2003; Boyd Haley, DAN Conference, 2003. Mercury contamination of waters, even at low levels can have very serious health effects as inorganic mercury can be converted as it ascends the food chain into the much more neurotoxic organic mercury compounds, methyl and ethylmercury. Minamata disease was a consequence of just such a conversion together with a massive increase in concentration of methylmercury in shellfish which formed a significant part of the diet of people living around Minamata Bay, Tsubaki and Irukayama, 1997. Mercury contamination of tuna, swordfish and other large game fish is now a public concern and limits the consumption of these fish which provide a supply of essential omega-3 fatty acids.

Arsenic is much more widespread in the human environment than thought earlier. Water supplies are contaminated with high levels in many parts of the world and can reach toxic levels leading to all the classical symptoms of arsenic poisoning- this is especially so in places like Bangladesh, but arsenic levels are high in many countries including the USA. Recommended levels have been reduced downward to 10 ppb, parts per billion, WHO 2001.

Dr Dick Van Steenis has made several studies of releases from waste incinerators and crematoria that result in the release of toxic heavy metals and other particulates below 2.5 microns. These particulates enter the deep lung and effectively carry toxic material into the body. Carbon particulates also provide a potent source of destructive free radicals and are known to be very damaging to health, see *inter alia*, Van Steenis 1999, 2002.

Dr Chris Busby, 1995, 2000, 2003, of the low level radiation campaign, www.llrc.org ,in co-operation with scientists from all over the world has produced a major report, ECRR, 2003, that re-assesses the health effects of ionising radiation released from nuclear test programmes and the nuclear industry. The report calculates that the adverse health effects from such exposures to be responsible for 62 million extra deaths worldwide. A high price for the failed nuclear experiment.

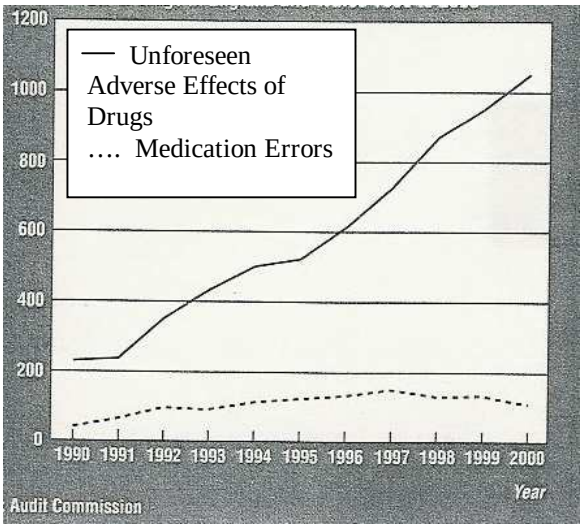


Figure 2. Numbers of Deaths from Medication Errors (wrong drug or dose) and from UNFORESEEN Adverse Effects of Drugs in England and Wales – 1990-2000.

The adverse effects from modern drugs are rapidly increasing and almost certainly under-Reported, Eaton, 2002. Figure 2 shows a six-fold increase in deaths from unforeseen adverse effects for compounds that have been extensively investigated and for which considerable toxicological data will have been collected and trials on healthy and sick people carried out. Even with all this careful science unexpected and serious events can occur.

In summary, our environment is grossly polluted with a wide variety of chemicals and we have virtually no understanding of the toxic effects of most of them. There is considerable evidence to show that many can cause adverse health effects and their use should be seriously limited or the compounds withdrawn. We continue to release novel chemicals into our environment as we seek ever more technological fixes for real or imagined problems. The latest involve potent broad spectrum herbicides, novel nucleic acids, and proteins associated with the production of GM crops.

It is important to recognise that usually only individual chemicals are usually tested. However, the exposure of the public is to the active chemical formulated in a finished product. This introduces further toxic possibilities. The other products in the formulation may be toxic themselves and/or act synergistically with the active compound to massively increase its toxicity. This was certainly the case with organophosphate pesticides which were formulated with known toxic compounds such as phenols, chlorophenols, epichlorhydrin, and organic aromatic hydrocarbons such as toluenes and xylene. The phenols were withdrawn from the formulaton in 1993. Another example is the identification of the cardiotoxic properties of the surfactant used with glufosinate a herbicide which is widely used with some GM crops, Koyama et al, 1997, Very often it is impossible to discover the exact chemical nature of compounds used in formulations of an active compound- crude mixtures of compounds are commonly used, trace impurities are unknown and only the general properties of these compounds are known.

MCS is one consequence of widespread distribution of numerous novel chemicals, usually in complex and often ill-defined mixtures, many of which may trigger a response either initially or following the development of full-blown MCS.
The whole environment, soil, water, air, and food, is contaminated and drastic action is required now to redress the present very unsatisfactory situation.

TRIGGERING MCS.
Many people with MCS can identify an event when they suffered a large exposure to a toxic chemical such as a pesticide being sprayed outside or in the house. Sometimes it may be a result of treatment of and adjacent property or a roof space where assurances are given that the material "is safe". This is followed by an increasing sensitivity to the same or related chemicals then finally to quite diverse chemicals in very different situations. Among Gulf War Veterans, GWVs, an increased incidence of chemical and multiple chemical sensitivity, Wessely et al 2001, Proctor, 2000. More than 40 possible battlefield exposures, 1990-1, have been identified, IOM, 2000, with the major ones being vaccines, pyridostigmine bromide (anti-nerve agent prophylaxis), pesticides (organophosphates, pyrethroids, lindane), nerve agents (sarin, tabun, VX), depleted uranium, oil and smoke, Hooper, 2000. Frequently chemical sensitivity developed to perfume, worn by wives, children, and girl friends and previously enjoyed by the veteran, and/or to petroleum fumes which had previously not been a problem, Miller, 2000; Meggs1999. The chemistry of perfumes and petroleum products is extensive and variable but very different from the chemistry of the pesticides and vaccines and other major Gulf exposures.
However, chronic low dose exposure to chemicals which may not be apparent to a person can also lead to MCS.

WHAT IS GOING ON?
The conundrums posed by MCS require new understandings of the processes in the body that handle foreign chemicals. Major considerations are-

1. Metabolism of foreign compounds in the body.
    - **a.** The liver is the main organ of metabolism which generally takes place in two stages. Other metabolic sites in the body include the gut wall and there are small contributions from other sites.
    - **b.** Phase 1 proceeds by oxidative processes involving cytochrome P450 enzymes which can be induced to cope with a high load of a foreign compound or by some drugs or chemicals, eg. Barbiturates. They may also be inhibited by some chemicals or drugs, eg. Cimetidine – this may lead to increased toxic effects.
    - **c.** <u>These enzymes are under genetic control</u> and this genetic variability, known as polymorphisms, provides an understanding of why some people are more susceptible to or handle some chemicals better than others.
    - **d.** These enzymes generate highly reactive intermediates that are commonly free radicals with considerable potential for causing tissue damage.
    - **e.** In Phase 2 metabolism these Phase 1 reactive intermediates rapidly combine with a variety of simple compounds, sulphate, amino acids, glucuronic acid to form compounds that are much less reactive and generally more water soluble that can be excreted in the urine. An

important secondary route of excretion, especially for more fat soluble compounds, is via the bile and thence into the intestinal tract.

f. If Phase 1 metabolism outstrips the capacity of Phase 2 metabolism there will be a build up of reactive oxygen species. The ensuing oxidative stress will have severe adverse health effects. Some 80% of ME-CFS patients suffer from oxidative stress as a result of major detoxification problems, Rigden, 1999.

g. If the threshold triggering enzyme induction is raised, for whatever reason, then toxic compounds would accumulate in the body and removal would be slow, Mellish, 2001 and undated.

2. Allergy and MCS

The association of MCS with allergy has been the subject of considerable debate mainly concerned with the definition of allergy. One common scheme recognises four kinds of allergic/hypersensitivity reactions, Kuby, 1997.

a. Type 1- is mediated by immunoglobulin E. IgE and is almost immediate, 2-30 minutes, and leads to systemic anaphylaxis which can be life threatening or to more localised anaphylaxis, insect bites, hay fever, asthma, hives, eczema, food allergies. IgE interacts with specific cells, basophils and mast cells that arstimulated to release potent vasoactive mediators such as histamine, leukotrienes etc.

b. Type 2- is antibody-mediated. The antibodies, IgG and IgM, attack sites on cell walls leading to total destruction of the cell. This process takes longer, 2-8 hours. The cell damage/loss can be very serious, examples include blood transfusion reactions and some types of anaemia.

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

d. Type 4-cell-mediated hypersensitivity is slow, 24-72 hours, and involves sensitised immune cells, special T cells, that release chemical messengers, cytokines, which activate other immune cells causing direct cell damage. Contact dermatitis, tubercular lesions, graft rejection are examples of this type.

Not uncommonly a single chemical or group of chemicals can induce more than one type of allergic response, eg. penicillins can cause type 1-4 type reactions.

3. Meggs, 1999, sees allergy, defined as type 1 above, and MCS as opposite sides of the same coin which share a similar mechanism.

a. The response to an allergen or a chemical irritant is not limited to the immediate site of application or entry. For example, about 2% of asthmatics will have their asthma triggered by eating certain foods. The inoculation of the gut leads to a response in the lungs- Meggs calls this switching. Bee stings may cause a generalised reaction involving the whole body and not just the local area affected by the sting itself. Similarly, chemicals that are generally inhaled can cause diverse

symptomology associated with the central nervous system, headaches, pain, rashes,and gastrointestinal disturbances.

b. Adaptation is a key four stage construct in chemical exposures that has been known from the 1950s.

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

The removal of the offending chemical(s) will lead to recovery except at stage 3.

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

d. Essentially, chemical irritants bind to receptors on unmyelinated sensory nerve C-fibres which are found in the gut, airways, eye and genitourinary system and are more numerous in patients with MCS. Binding triggers the release of substance P (for pain) and other mediators of inflammation by interaction with mast cells, Figure 3 . The ensuing neurogenic inflammation can be switched to other sites in the nervous system, Figure 4.

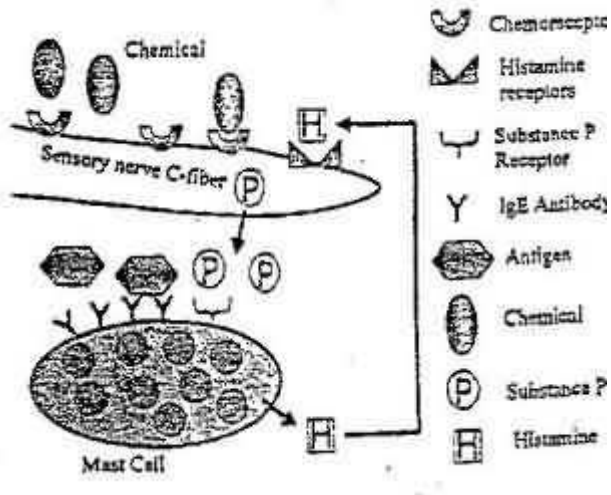


Figure 3. Binding of chemicals to C-fibres triggers inflammatory response.

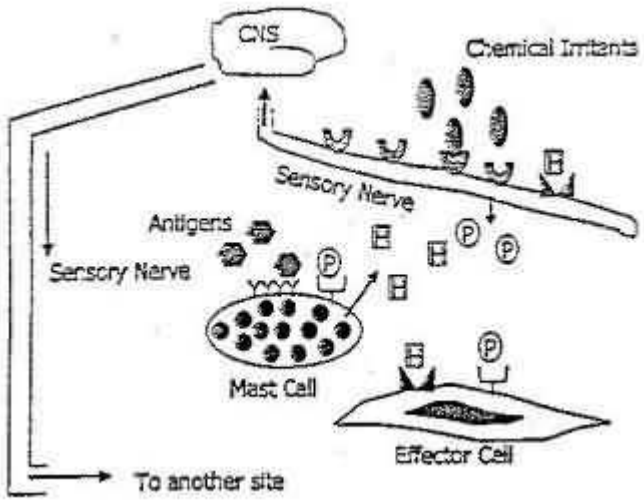


Figure 4. Switching of response via the central nervous system, CNS.

Meggs make much use of data from studies on GWVs and reports the extensive intolerance to petrol, diesel and oils as well as exhaust fumes. Many veterans describe their response as loss of awareness ('spaced out'), loss of motor control and ataxia. In some cases this was so marked that driving became dangerous. Some veterans are now unable to fill up their vehicles at a filling station because this would render them incapable of driving safely.

Mortality studies on GWVs show that there is an excess of deaths from motor vehicle accidents. Whilst this has been dismissed by the MOD and DOD (Department ofDefence, USA) as a legacy of military service resulting in extravagant and risk taking behaviour and an inability to cope with a return to civilian life no other explanation has been forthcoming. MCS offers another explanation that better accords with the evidence and military training which requires extravagant risks be avoided and makes motor control and awareness paramount.

4. TILT- toxicant-induced loss of tolerance.

Ashford and Miller, 1998, and Miller, 2000, introduced this novel concept in which a common mechanism is postulated for both drug addiction and multiple chemical intolerance (their name for MCS) but with opposite responses- addiction (a demand for regular and repeated doses) and abdiction (avoidance of a substance). In both cases the intent is to avoid withdrawal symptoms that are associated with lack or presence of the substance. The basic idea is set out in Figure 5 in which the normal response to a stimulant (eg. caffeine) involves stimulation followed by recovery. Loss of tolerance leads to an increased response that leads to alternative strategies, abdication (avoidance) or addiction (persistent reinforcing doses).

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

Another aspect of the proposed relationship between abdiction and addiction is that dopaminergic, 5-hydroxytrypamine, 5-HT, and opioid neural pathways in the brain are associated with addiction and the response to addictive drugs and food. These same pathways are damaged in GWVs – see below.

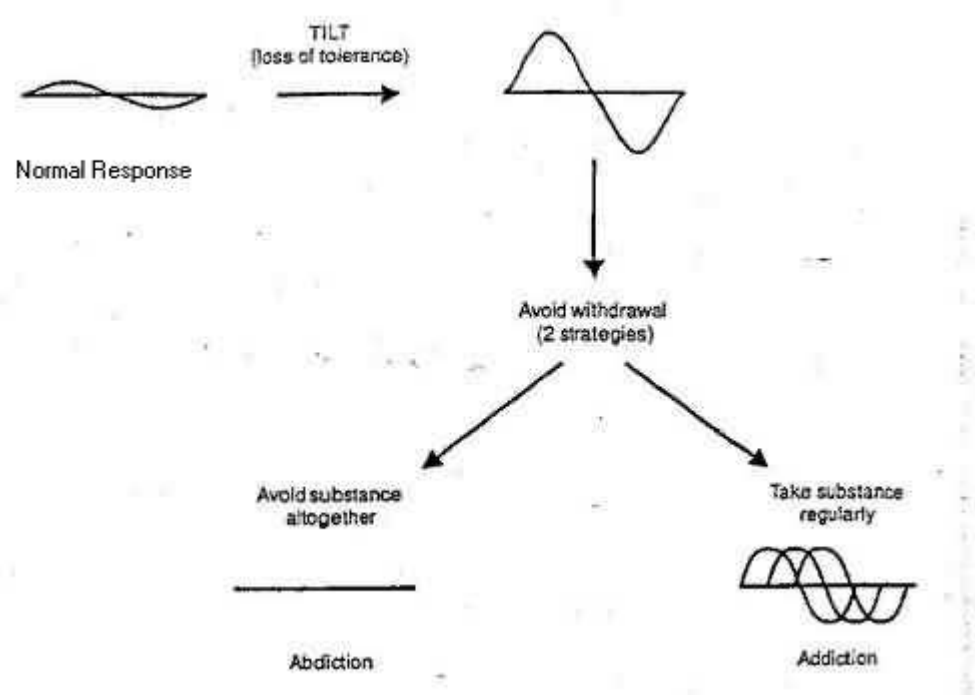
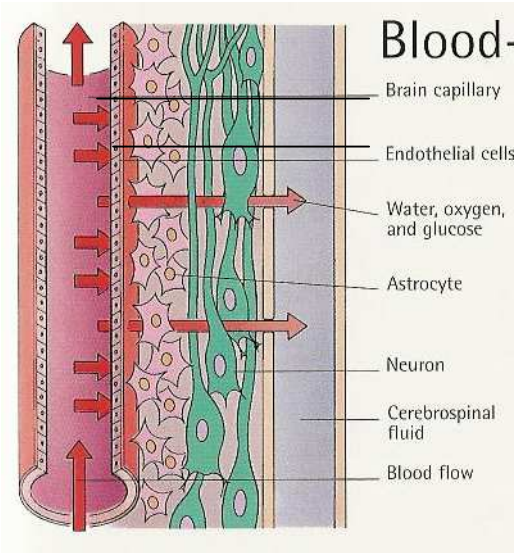


Figure 5. TILT – relationship between abdiction and addiction

Ashford and Miller, 1998, also draw attention to the transport of volatile or aerosolised inhaled substances by intraneuronal transport along the olfactory tract directly into the limbic system. This by-passes the blood-brain barrier and introduces compounds directly into deep (silent) brain structures where many basic bodily responses are controlled. This part of the brain is also called the 'reptile' or palaeolithic brain since similar structures with similar functions are found in many lower animals.

5. The Blood-Brain Barrier.



This refers to the endothelial cells lining the blood vessels in the brain, Figure 6. The cells possess tight-cell junctions that severely restrict access of compounds from the blood into the brain. This is a protective mechanism to restrict entry into the brain of biological and chemical toxins that may be ingested, inhaled, or generated by infection, in other parts of the body or by injury. There are selective transport mechanisms that supply neuronal and other cells with essential nutrients.

Tight cell junctions occur in other tissues

particularly the gut and the lungs. This protection limits transport across the gut wall- toxins and infections in food and water- and the lungs – inhaled toxins.

Figure 6. The Blood-Brain Barrier.
The by-passing of the blood-brain barrier by intraneuronal transport via the olfactory bulb allows toxins direct access into the brain.

Tight cell junctions can be opened by a number of bacterial and viral toxins and by some chemicals including organophosphates and pyrethroids even at very low concentrations. A very recent *in vivo* study in mice using advanced mass spectrometry techniques, Vogel et al, 2002, found that doses of parathion or permethrin at attomolar, 10^{-18} molar, concentrations opened up the blood brain barrier and increased, by ~20%, transport of a marker compound, diisopropylfluorophosphate, into the brain. These tiny quantities correspond to the amount of residue that would be found on a single apple following spraying.

The blood-brain barrier is lest efficient in the region of the paleolithic brain and any leakage through the barrier will be greatest in these regions, basal ganglia, brainstem and thalamus.

The opening of tight cell junctions at one site is often accompanied by opening of tight cell junctions at other locations, for example, in asthma the gut junctions are opened up giving rise to increased gut permeability. Organophosphates will increase gut permeability as well as opening the tight cell junctions of the blood-brain barrier.

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

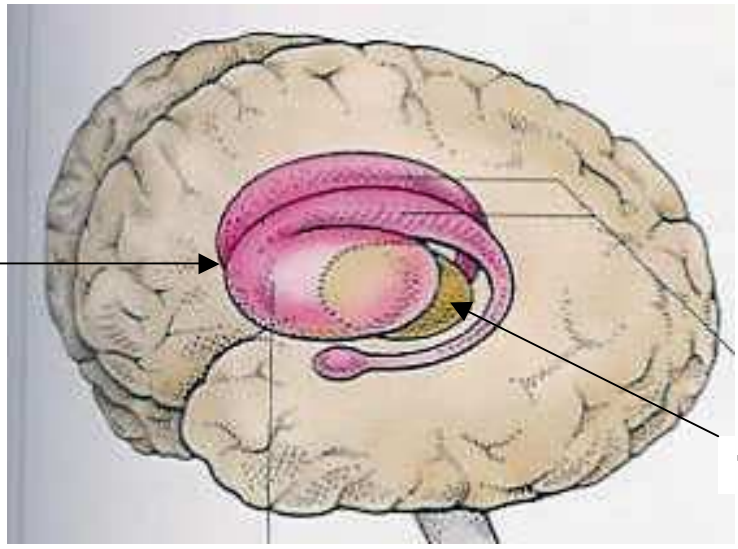
6. AN ALL ENCOMPASSING MODEL FOR OVERLAPPING SYNDROMES

The incisive research of Dr Robert Haley with Gulf War Veterans, Haley, *inter alia* 2000, 2002 has identified cellular damage to the deep (silent) brain structures, the basal ganglia, and the brain stem, Figure 7. Using magnetic resonance spectroscopy he found about 25% of cells in these areas of the brain were dead. The basal ganglia located deep in the brain and composed of several different nulcei initiate and control movement sequences, such as walking and other voluntary movements carried out unconsciously. They wrapped round the thalamus that sits at the top of the brain stem. The thalamus is a relay centre for sensory nerves and relays signals coming via the spinal cord and brainstem to the higher areas of the brain. It is particularly involved in pain sensations.

Figure 7. Basal Ganglia wrapped round the Thalamus deep in the Brain.

The brain stem, Figure 8, is composed of the midbrain, pons, and medulla. The midbrain controls visual and auditory reflexes and damage here would make for photophobia and aversion to noise. The pons is concerned with facial expressions and eye movement- nystagmus is quite commonly found in ME and related overlapping syndromes. The medulla regulates heart rate, blood pressure, digestion- swallowing and vomiting, respiration and temperature. Most of these functions are disturbed in the overlapping syndromes. Balance and orientation associated with brain stem function are also noticeably affected.
Haley described the symptoms found in GWVs as arising from damage to those parts of the brain that are known to be damaged in Parkinson's disease and other diseases such as, Huntingdon's chorea, Fahr's and Wilsons disease. Parkinson's disease involve significant loss of dopaminergic neurons. This accords with Miller's suggestion that addiction and chemical sensitivity might be closely related.

The cause of this damage Haley put down to chronic exposure to low levels of nerve agents, particularly sarin gas. Sarin is an organophosphonate that is similar, in structure and biological activity, to organophosphate pesticides that were widely used in the Gulf War 19990-1. Both these groups of chemicals (together with pyridostigmiine bromide- NAPS tablets) attack the cholinergic nervous system



producing a devastating 'triple whammy', Hooper, 2000. A cholinergic neurone plays a crucial regulating role in controlling the activity of the dopaminergic, glutaminergic and gabaminergic neurones associated with Parkinson's disease, and Huntingdon's chorea, the basal ganglia, Kruk and Pycock, 1991. Cheney and Hyam, 1999, describe ME-CFS as 'cholinergic wipeout'.

Richardson 2001, describes a 15-year old boy with frank parkinsonian symptoms following a virus infection and Bruno, 2002, describes, in some detail, the damage to dopaminergic neurones in the basal ganglia that is caused by the polio virus.

Goldstein, 1999, describes ME-CFS as a limbic encephalopathy brought about by viral infection. The limbic system is encircles the basal ganglia and is part of the deep (silent) brain structures, Figure 8.

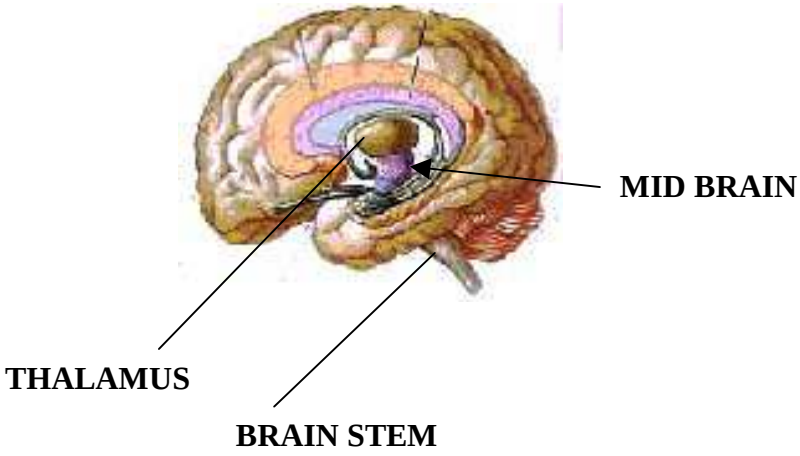


Figure 8. The Limbic System encircles the Basal Ganglia (not shown in this cut away) which enclose the Thalamus at the top of the Midbrain,part of the Brain Stem.

The limbic system is also the area of the brain that is most affected (damaged) in multiple chemical sensitivity, Ashford and Miller, 1998. It is composed of a number of brain regions including the amygdala, particularly associated with aggression, the hippocampus associated with learning, recognition and memory (some GWVs have reduced hippocampal mass), and hypothalamus that drives the pituitary gland and the endocrine system. The activities of the body that are governed by the limbic system are concerned with self-preservation (hunting for food, fighting) preservation of the species (sexual behaviour and rearing of offspring) fear, rage and pleasure and the establishment of memory patterns. Loss, or partial loss, of these functions is common amongst ME sufferers.

An important part of the limbic system is the olfactory bulb, Figure 9. Volatile chemicals and odours are transported intraneuronally, via the olfactory bulb and nerve, directly into the limbic system. The problems of smells and odours are all too common in ME and the other overlapping syndromes.

Acetylcholine is a major neurotransmitter in the limbic system and it is not surprising that exposure to OPs, and nerve agents used in chemical warfare cause serious deficits in this system.

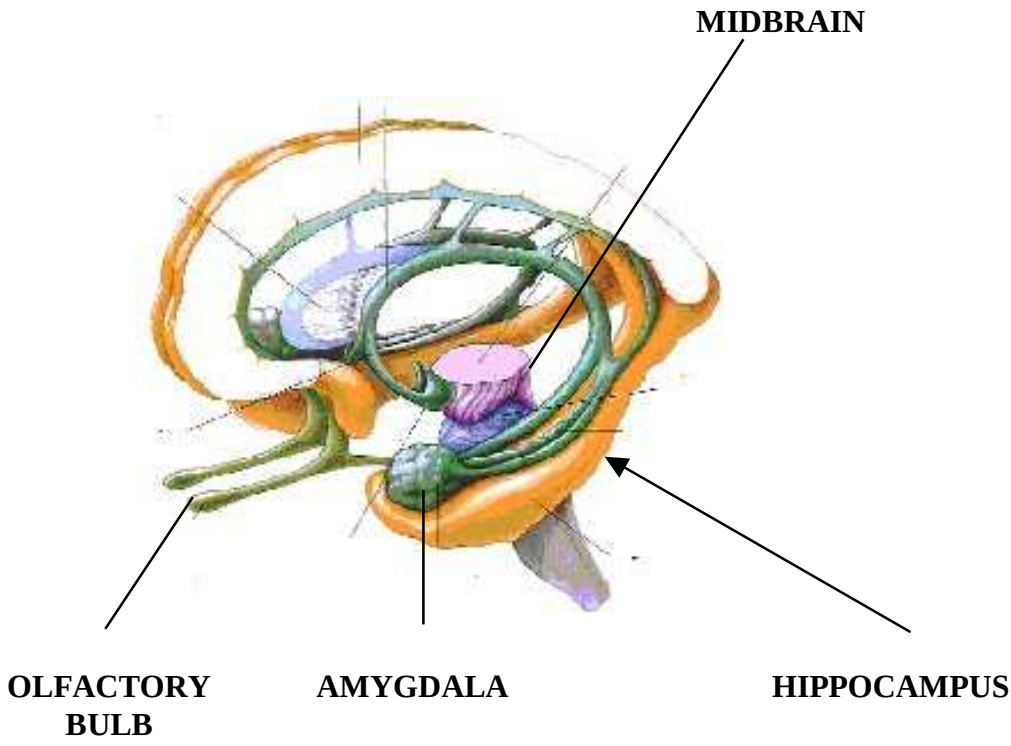


Figure 9. A cut away view of the Limbic System

Neurological damage as a result of toxins, biological or chemical, entering the deep brain structures would give rise to the symptoms common to all the overlapping syndromes.

It is now clear that certain chemicals and biological toxins cause the tight cell junctions to open and allow these toxic materials to enter the brain. The BBB is least efficient round the primitive brain regions, described above, making movement of toxins into these areas of the brain easier. Volatile compounds are transported intraneuronally directly into the deep brain areas via the olfactory bulb, thereby bypassing the BBB. The deep, silent, brain regions are more susceptible to damage from all environmental toxins.

The common symptoms are associated with common pattern of injury to the deep areas of the brain, the brain stem, thalamus, basal ganglia, and the limbic system provide a coherent explanation for all the overlapping syndromes.

- ME may arise from a number of different viral infections. The inflammatory response to viral infections resulting in endothelial damage provides an indirect but devastating mechanism for damage to the central nervous system. The recent comprehensive model, for ME-CFS, fibromyalgia, multiple chemical sensitivity, post traumatic stress disorder, that involves glutamate receptor sensitisation by excessive release of nitric oxide and its highly destructive derivative, peroxynitrite also fit this scheme, Pall, 2000, 2002; Pall and Satterlee, 2001. It is noteworthy that nitric oxide also has a major role in intestinal inflammation, Kubes and McCafferty, 2001. Nitric oxide also plays a major role in the cardiovascular system where it causes vasodilatation and a fall in blood pressure.

- PPS, post polio syndrome, arises from polio virus and allied enteroviruses, Richardson, 2001, Dowsett, 2003.
- Organochlorine poisoning from excessive exposure to organochlorine pesticides, Richardson, 2002.
- OP poisoning from excessive exposure to this class of pesticides. The role of synergy with other chemicals that occur together in pesticides and mixtures of pesticides is associated with a massive increase in toxicity, Abou-Donia et al, 1996; Abou-Donia, 2001.
- Multiple chemical sensitivity from exposure to toxic chemicals or combinations of toxic chemicals, Ashford and Miller, 1998; Miller, 2000, Meggs, 1999, Donnay, 2000.
- Fibromyalgia can be regarded as a variant of ME that is associated with excessive neuromuscular pain.
- Gut dysbiosis and irritable bowel syndrome provide an alternative source of toxins, Butt et al 2001.

7. Some Preliminary Conclusions

Using our IAG test we have data on more 100 people some diagnosed with MCS but others with ME-CFS, organophosphate poisoning, and GWS who report increased chemical sensitivity to a variety of diverse compounds. From this data and through extensive contacts and discussions with people suffering from these syndromes and those professionals who were supporting them we have built up a picture of the common core of biochemical deficits shared by these different groups, Figure 1.

These deficits break down into 4 major groups.

a. Gut function and integrity

- **i.** One of the commonest features of the overlapping syndromes is a disordered gut. Restoring gut function is helpful to many with MCS.
- **ii.** The IAG test which results from aberrant tryptophan metabolism generating a potent and destructive compound, indolylacrylic acid. This compound which is metabolised to IAG arises from bacterial metabolism in a dysbiotic gut and indicates damage to the gut wall with increased permeability and compromised digestion, Hooper 2003; Shattock and Savery, 1997. Gut permeability is readily measured, Biolab, 2000.
- **iii.** Compromised digestion releases opioid fragments from proteins in milk and gluten, the casomorphins and gliadomorphins. These pharmacologically active peptides are carried through the permeable gut wall and can then exert their effects locally in the gut and at other sites particularly in the central nervous system. Digestive activity can be measured, Biolab, 2000.
- **iv.** The opioid excess theory of autism provides an understanding of these different processes and is summarised in Figure 10.

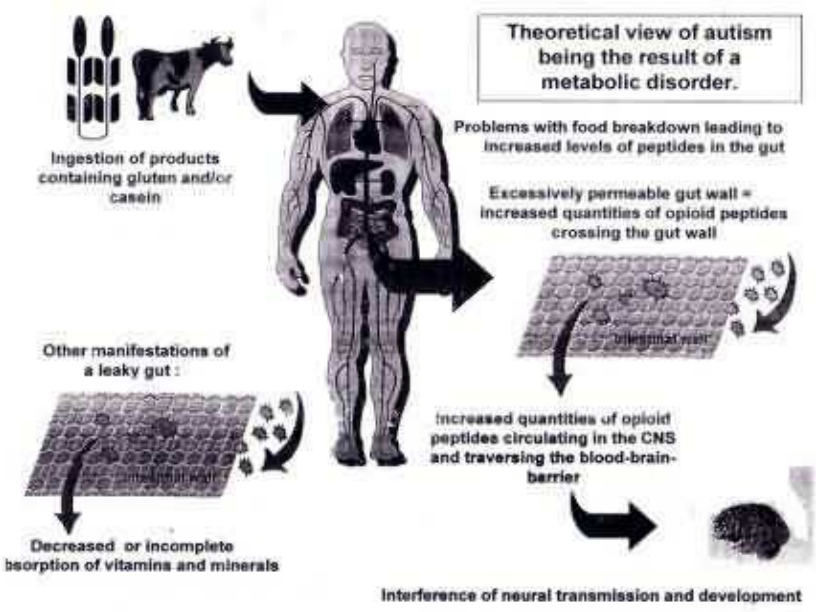


Figure 10. A Summary of the Opioid Theory of Autism following increased permeability of the Gut Wall.

v. The schematic diagram at Figure 11 shows the importance of the central role of opioids in communication between the neuroendocrineimmune systems. The balance between these systems is essential for good health and any disturbance of this balance can lead to dysfunction in any of these systems and give rise to the constellation of symptoms commonly found in all the overlapping syndromes.

vi. The production of 5-HT, an important neurotransmitter in the gut and CNS, is reduced as a result of disordered tryptophan metabolism. It also plays an important role in endocrine function, Richardson, 20001.

vii. Useful and practical steps can be taken to correct all these problems in the gut- see treatment below

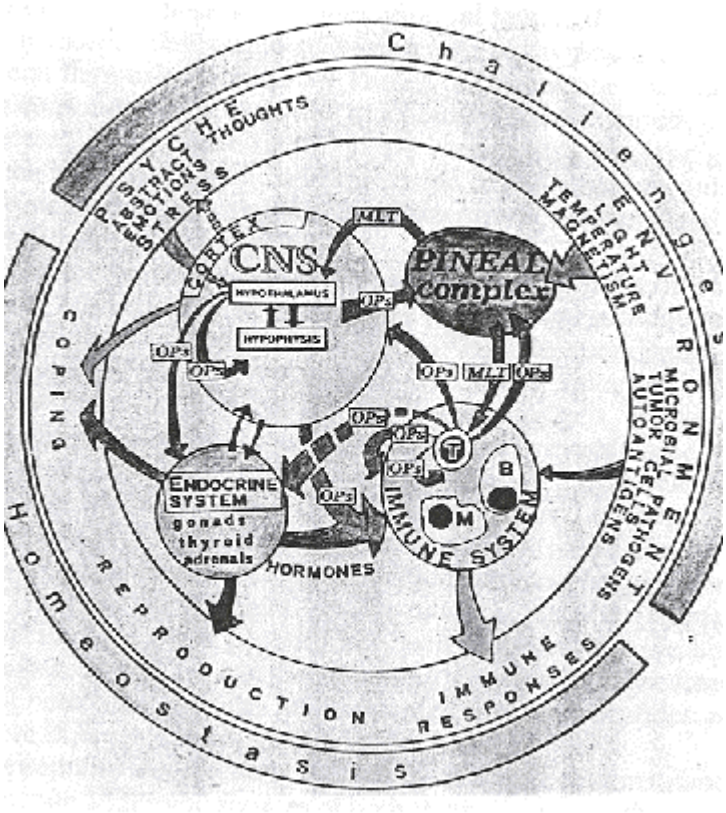


Figure 11. Schematic showing the role of Opioids (OPs) in the communications between the Neuro (CNS), **I**mmune, and Endocrine Systems, Ader, 1991.

b. Sulphur metabolism, detoxification, and Membrane Integrity.

- **i.** Sulphate metabolism is part of the major Phase 2 metabolic processes that is especially important in the removal of phenols and amines from the body. It is known to be disturbed in MCS and other overlapping syndromes. The measurement of serum levels or urinary sulphite is diagnostic. If sulphate levels are low and there is sulphite in the urine this indicates a specific failure of an enzyme, sulphite oxidase. This enzyme is dependent on a molybdenum a co-factor for the enzyme and can readily be supplied as a supplement.
- **ii.** Sulphate is mainly synthesised in the body from the essential amino acid cysteine. The cysteine cycle serves many other purposes and is dependent upon the presence of folates and vitamin B12. It is possible to check the functional status of the cysteine and methionine cycles and correct any deficit of these vitamins.
- **iii.** Sulphate is an essential component of key membrane-associated macromolecules, glycosylaminoglycans (GAGs). These molecules maintain a negative charge on the membrane and serve also as hydration sites which maintain the properties of mucous membranes, Owens, 1998; Hooper, 2003.

iv. Some GAGs play special roles in controlling blood clotting and the immune response.

v. Sulphation is a key process in controlling the balance of key pharmacologically active molecules, DHEA (dehydroepiandrostenone) which is the major steroid stored in the body and chlolecystokinin which is the most abundant neuropeptide in the brain and also has a key role in gut function.

vi. Thiols are key compounds in maintaining the redox potential of cells and in counteracting oxidative stress. The key intracellular molecule is glutathione which is synthesised from cysteine.

c. Polyunsaturated Essential Fatty Acids, PUFAs.

i. These are required to maintain normal membrane structure and function and form an integral part of the central core of most membranes throughout the body.

ii. They also provide essential precursor molecules for key compounds associated with the inflammatory response which may be pro- or anti- inflammatory.

iii. There are two classes of PUFAs, the omega-3 oils, found in fish and flax seed oil, and the omega-6 oils found in most plant oils eg evening primrose oil. It is now recognised that it is the balance between the omega-3 and omaega-6 oils that is important.

iv. The measurement of PUFAs in red blood cell, RBCs, membranes provides a quantitative measure of these important compounds, Biolab 2000. An indirect measure of any deficit is provided by assessing the proportion of mishaped RBCs in a fixed blood smear, Simpson, 1989a,b; Spurgin, 1995.

d. Trace Element and Vitamin Status

i. Although it is possible to make recommendations about nearly all the essential elements I have selected the following as the most commonly mentioned.

ii. Magnesium- this is not really a trace element but it is often low in many people with ME-CFS. Magnesium plays an essential role in a huge number of key biochemical processes. It can be measured in RBCs.

iii. The genuine trace elements of greatest importance appear to be, selenium and zinc. Both can be readily measured. Several papers have reported the low to very low selenium levels in the population as a whole, Rayman, 1997, 2000. The levels are so low that there is now a strong case for supplementing general foods with this element in a suitable form. Selenium plays a key role in thyroid function (conversion of T4 to T3) and in important detoxification enzymes (glutathione transferases) as well as other enzymes. Molybdenum has already been discussed.

iv. Zinc is required to combat infections, particularly viral infections.

v. The key vitamins are B1, B6, B12 and folates, C (ascorbic acid), E, and carotenes. The last three are essential components of the anti-oxidant cascade and are useful in combating oxidative stress.

I am aware that many other proposals can be made and many can be justified from literature reports and/or the experiences of people suffering from one or more of the overlapping syndromes. Figure 12, provides a summary of the possible biochemical deficits and the supplements that will correct them. I have highlighted what appear to be the most important general factors but this cannot replace the judgement of a wise physician or nutritional therapist.

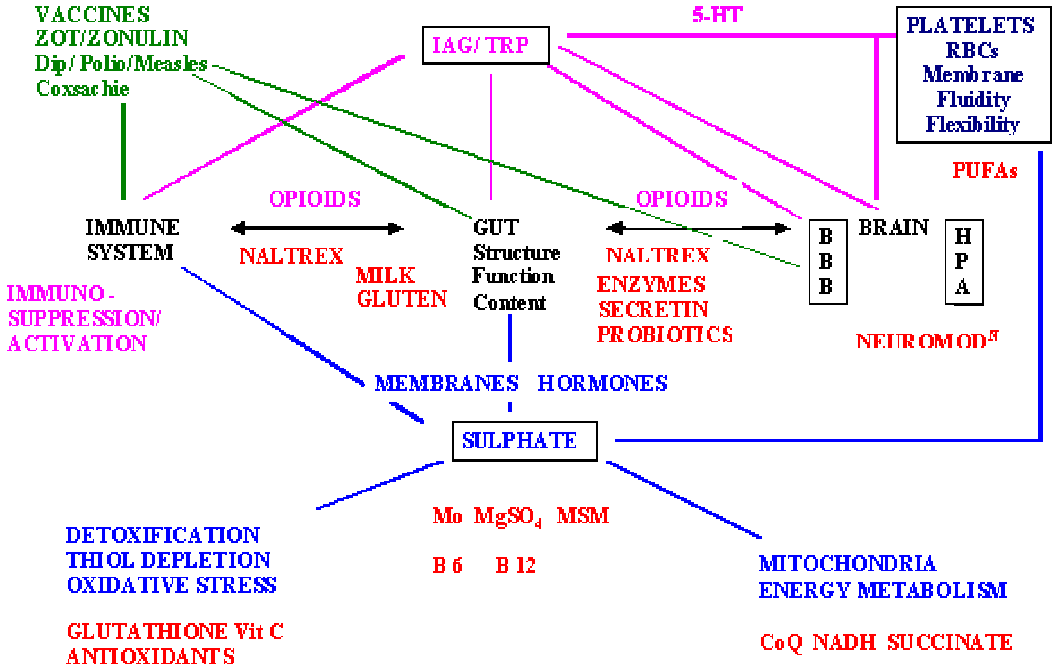


Figure 12. Composite of Interactive IAG/TRP-Sulphation/Sulphur and PUFA Systems with Treatment Summary in red letters.

8. Treatment

Detoxification techniques have been pioneered by Rea and others and include, environmentally controlled accommodation with strict control of air and water to unmask toxic effects and a variety of heat depuration procedures and desensitisation techniques allied to nutritional medicine, Rea, 1998, BSAENM, 1997, 2000.
Our approach involves

Correcting Gut Function and Structure Problems.

i. The 4Rs. A stepwise approach is summarised by the following

- Remove – problem foods- milk/dairy (3weeks) and/or gluten containing foods (8 months).
- Replace – key enzymes proteases, lipases etc. There are good prescribable products available.
- Re-inoculate with key gut bacteria such as lactobacilli, bifidobacteria. These are found in live yoghurt preparations and are also supplied as freeze-dried preparations in capsules
- Repair – glutamine is a key repair molecule in the gut. It is readily available and easy to take.

ii. A more extensive programme, known as the Sunderland Protocol**,** is available at http://osiris.sunderland.ac.uk/autism . This includes a food diary for identifying other food intolerances.

b. Addressing Sulpur metabolism and Sulphation problems.

i. The use of Epsom salts, magnesium sulphate, addresses both magnesium and sulphate deficiency. Small oral doses of magnesium sulphate BP (a product that complies with the standards of the British Pharmacoepia) may be all that is needed. It is best to use a dose of around 600mg (1/3 teaspoonful) in water once or twice a day with food. Alternatively, Epsom salts can be placed in the bath water (couple of handfuls of the cheaper grade of commercial Epsom salts).

ii. Magnesium and sulphate are not readily absorbed orally or through the skin but the above regimen will provide a sufficient supply for most people- others may need intravenous infusions. Larger doses of magnesium sulphate are used as a purgative so if a watery diarrhoea develops then the dose should be reduced or an alternative source of magnesium and sulphate used. Too much magnesium may lead to adverse effects some of which are known to be serious so small doses and regular monitoring is strongly advised. Once normal levels of magnesium and sulphate are reached then no further treatment is necessary. Onion, garlic and broccoli are good food sources of sulphur and green vegetables of magnesium.

iii. Other preparations of magnesium salts are available but much more expensive eg. the glycinate. Sulphur can be supplied as MSM (methylsulphonylmethane) but there are concerns about the use of this compound, Owens, 2003- personal communication.

iv. Vitamins B12 and Folates play an important role in sulphur metabolism and need to be provided following the assessment of functional levels of these compounds. It is important to provide both series of compounds. The dosage regimens are often well above those commonly employed and of the order of 1,000-5,000 micrograms per day for at least 1 week for B12- best as hydroxycobalamine - by injection or buccal absorption. Folate can be given at 2.5 mg daily for 1 week.

v. Methylcobalamine, the final form of cobalamine in the sulphur-methylation cycle is now available in the USA and widely advocated as the ultimate treatment. This is provided in “insulin” syringes for self-injection and offers some advantages. It is a rather unstable compound and only quality assured products should be used. They are expensive, DAN, 2003.

c. PUFAs – essential fatty acids.

i. The importance of essential fatty acids is recognised in the Sunderland protocol and important sources indicated.

ii. It is now clear that it is the balance of omega-3 (fish oils and flax oil) and omega-6 (plant seed oils, eg. evening primrose oil) is important. A number of commercial formulations include both types of PUFAs

which play an important role in the production of pro- and anti-inflammatory mediators, prostaglandins and leukotrienes.

iii. It is important to Cod live oil has the added advantage of providing vitamin A in addition to the fatty acids. However, there are proper questions about vitamin A toxicity so the dose is important.

iv. It is important to ensure that all products containing PUFAs are free from pesticide and mercury contamination and contain a protective anti-oxidant such as vitamin E to prevent the rapid degradation that occurs in air.

d. Minerals and Vitamins

i. Magnesium has been covered above.

ii. Selenium is readily available in a variety of forms that will ensure assimilation and an appropriate dose is given on most formulations.

iii. Zinc is similarly available.

e. Thyroid deficiency

i. Very commonly patients suffering from any of the overlapping syndromes are described as biochemically euthyroid (normal) but often regarded as clinically hypothyroid (excessive and disabling fatigue, low level of alertness, weight gain, dry skin and hair, brittle nails, emergence of autoimmune disorders, etc). This contradictory picture is usually based on the measurement of blood levels of TSH (thyroid stimulating hormone) and T4 (thyroxine). However, the most important and potent thyroid hormone is T3 which is formed in the body from T4 by deiodination by a selenium-dependent enzyme. If this process is faulty then thyroid function will be dangerously compromised. Low levels of free, circulating thyroxine and raised receptor resistance can also contribute to a hypothyroid state. The complex factors involved with hypothyroidism have recently been recognised, Dayan,2001, Shames and Shames, 2001. All these different steps need to be checked out before normal thyroid function is accepted in an ME patient. It is a matter of the examining physician backing his clinical judgement against the biochemical data supplied from the laboratory.

ii. It is now clear that the conventional blood tests provide only a snapshot of thyroid status. An older and more reliable test involves a 24-hour urine test, particularly for T3, that is both more sensitive and reliable, Baiser et al, 2000; Downing, 2000

f. Other Factors.

i. I am aware that many other factors may be important but the above cover the most common and most basic in my limited experience and quite far-reaching contacts with various groups suffering from overlapping syndrome illnesses.

ii. Mitochondrial support, N-acetyl-L-carnitine, lipoic acid, and Co-Q, Liu et al, 2002, is important but I believe that it is best addressed after the above treatments have been explored.

Conclusions

The widespread use of chemicals of unknown toxicity has jeopardised the health of the environment and people throughout the world. Hubris and complacency have prevented a search for deeper understanding of human and environmental systems and led to increasingly risky attempts at technological fixes that have increased the level of damage and danger to this and future generations by increasing the toxic burden of unknown chemicals. Without a profound change of heart and mind in every major human institution then we shall inevitably regress into evermore destructive situations. The important changes will encompass and demand all the energies of all human societies and communities, medicine, science, farming, commerce, government, military and, above all, the ordinary people of the land in every nation.

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6th August 2003
