Health conditions associated with low levels of exposure to chemicals

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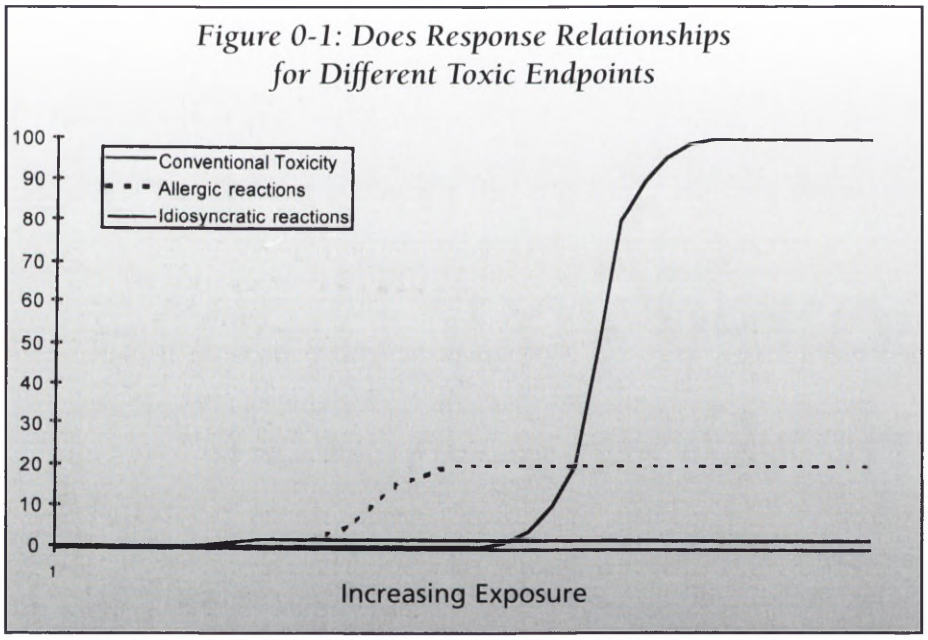
The dose response relationship

Sensitivity to chemicals can vary from individual to individual. It is generally considered that conventional responses to toxic exposures in a population are normally distributed - some people can be quite tolerant to certain exposures, while others may be quite sensitive. This is the basis of one the fundamental toxicological principles, the dose-response relationship (see the thick curve in Figure 1).



As well as conventional responses to toxic exposures, it is also recognised that some people (perhaps up to 15-20% of the population) show allergic responses to low levels of chemical exposures, and that these responses can be identified through measures of immunological or allergic function (also shown in the dotted line in Figure 1).

However, a third category of response is becoming recognised, in an even smaller group of people (maybe 1-2% of the population) of an idiosyncratic sensitivity to chemicals at very low exposures, for which physiological or medical indicators are not yet available (shown in the thin line in Figure 1).[1]

It is important to realise that in allergy and hypersensitivity responses it is not the type of response that alters in these cases, it is the level of exposure. For example, a person who idiosyncratically responds to, for example, a solvent shows solvent related effects, but at a much reduced exposure. They show nervous system related effects, and don't necessarily show symptoms in other body systems (such as in the skeletal system). For this reason, it should be concluded not that the possibility of such symptoms is remote, but that the dose response relationship needs to be shifted to the left to take into account such effects.

Establishing "acceptable" exposures in the workplace

The concept of the conventional dose response relationship is used to establish "acceptable" exposures to chemicals. In the occupational environment, attempts may be made to convert such acceptable exposures into permissible "exposure standards" set out in government recommendations, which may be incorporated by reference into enforceable occupational health and safety legislation.

Indeed, the Australian definition of exposure standard is:

the exposure standard represents airborne concentrations of individual chemical substances which, according to current knowledge, should neither impair the health of, nor cause undue discomfort to, nearly all workers. Additionally, the exposure standards are believed to guard against narcosis or irritation which could precipitate industrial accidents. Exposure standards apply to long term exposure to a substance or agent over an eight hour day for a normal working week, over an entire working life.[2]

The critical words in this definition are "nearly all workers", which are not defined quantitatively or qualitatively. There has been some debate by occupational hygienists about what these words mean, and it is concluded that the term nearly all workers does not include all workers, and that therefore exposure standards must be used with caution.[3] Further, because of the inclusion of the words "nearly all workers" in the definition of the exposure standard, it cannot be assumed that they are no observable effect levels (NOELs). Indeed, with inclusion of such words, they must be considered effect levels, at least for some workers.

Quite neatly, this definition incorporates the chemically sensitive worker into the scope of the exposure standard, without any real need to address whether the exposure standard is sufficiently adequate or protective (nearly all workers is not *all* workers). The words "nearly all workers" are therefore sufficiently imprecise to assist the occupational health practitioner to establish what is a safe exposure, without helping individuals who show susceptibility or sensitivity to certain expo-

sures. In this, the definition of exposure standard is flawed.

At the workplace level, the nature of the standard setting process for recommended concentrations of many workplace occupational contaminants has been questioned.[4]

Exposure to mixtures of chemicals

The exposure standard covers the situation where there is workplace exposure to one chemical. This hardly ever occurs. Mostly, people are exposed to more than one chemical at work, or in outside interests (such as hobbies) or even lifestyle activities (alcohol, smoking) can produce exposure to a range of chemicals.[5]

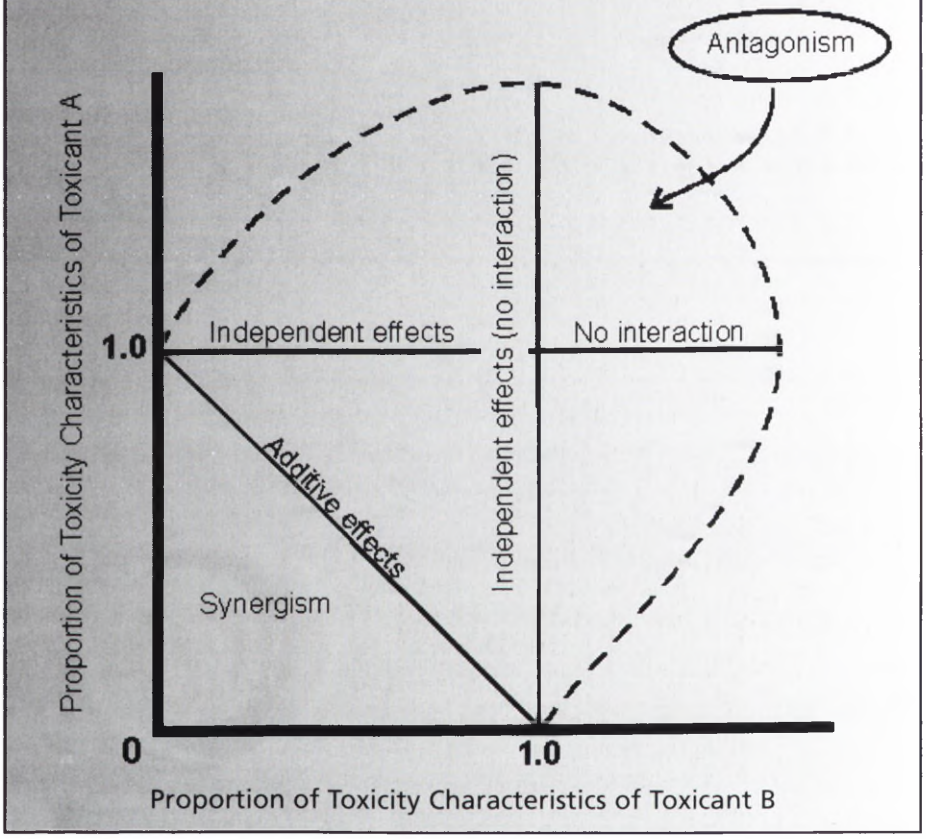
As well as the effects on single effects on the body, toxic effects will also arise from exposure to combinations of chemicals. Interactions between chemicals on exposure to mixtures is an area of some toxicological uncertainty. Mixed exposures can interact:[6]

- independently (no difference in effects);
- additively (effects equal to the sum of effects);
- antagonistically (effects decreased over what would be expected addively); and
- potentiatively or synergistically (effects increased over what would be expected additively).

Overall, the available knowledge on the types of interactions between chemicals, whether none (independent), antagonistic, additive, potentiative or synergistic is extremely small. The different types of interactions are shown graphically in Figure 2.

The operation of the exposure standard is problematic in multiple chemical exposures, because many are established just at the point the dose response relationship increases above a no observable effect level. In such cases, the margin of safety inherent in such exposure standards is so small that the possible contribution from other exposures could be sufficient to render the protection offered by the exposure standard illusive. Further, most exposure standards do not factor in exposure from routes other than inhalation (such as skin absorption). However, it is common practice in occupational hygiene to assume that the interaction of multiple exposures to chemicals at work can be estimated additively by summing exposures as a fraction of their exposure standards.[7] Implicit in this approach is that as the proportion of each contaminant in a mixture increases, the corresponding value for the exposure standard must fall (see Figure 2).

Figure 0-2: Types of Interactions



In a single exposure for a chemical that has an exposure standard, the recommended exposure standard is located at the point where the diagonal line cuts the x- or y-axis (the point 1.0 in figure 2 represents the multiple of the exposure standard). Where there are two (or more) exposures, and the interaction is additive, the relevant "composite exposure" (and the exposure standard it represents) must fall on the diagonal line in the figure above. This indicates that in mixed exposures, recommended exposure standards must *always be less* than the corresponding value for single exposures. If there are more than two exposures, then the slope of the line in the figure gets steeper.

If the interaction is synergistic, the composite exposure falls below the line in Figure 2, and the possibility of estimating a composite exposure standard is not possible.

While it is sometimes asserted that synergistic interactions do not occur at low non-toxic doses and therefore do not present a risk to health,[8] it has been repeatedly demonstrated that low, sub-toxic doses of chemicals in mixtures have been ▶

shown to enhance each others toxicity quite significantly.[9,10,11]

Further, the posssibility of a synergistic interaction becomes more likely the more chemicals are involved in the exposure. An approach which selectively ignores any possible synergistic interactions between the individual constituents in an exposure is fundamentally illogical.

Of what is known about interactions, it seems that most interactions, where they have been reported, are of the additive type. However, the few synergistic interactions that have been reported give significant concern about the effects of other possible combinations of chemicals.

It is difficult to define the role played by chemical exposures since other causative factors may intervene (such as tobacco and alcohol use, medication, pithiatic or immature personality, arteriosclerosis, head injuries, and so on). However, it is important to realise that these are real symptoms which can often precede chemically related disease (see Figure 3 below). They must be placed into a relevant context to have meaning. They cannot be dismissed merely because medicine or science is too imprecise to measure them.

Figure 0-3: The Development of chemically related injuries

Normal	Chemical exposures do not cause health problems.	
Sensitisation	Susceptible individuals are affected at low exposures to chemicals. Sometimes the mechanism of effect is allergic.	-algias
Irritancy	Mainly non-specific or subjective signs and symptoms at chemical exposures that are considered "acceptable".	-algias -itis
Inflammation	More specific signs and symptoms at or above acceptable exposure to chemicals.	-itis
Injury	Damage and injury to unacceptable chemical exposures. Poisoning and clinical disease.	-osis

Chronic Fatigue Syndrome

Chronic fatigue syndrome seems to be a two stage condition in which the first stage appears to be a "precipitating" component such as an infection or exposure to toxic chemical(s). This usually responds well to conventional medical treatment. However, the second stage of the disorder is a long term debilitation which appears to be out of proportion to the initial "precipitating event". This second stage also responds poorly to medical attention, leading to frustration in patients and the treating physician.

A definition was issued by the US Centers for Disease Control (CDC) in 1988.[12] A more restrictive definition was issued by the US CDC in 1995 (see Figure 4).[13]

Leaking fumes case puts airlines on alert

A court decision could prove to be costly for airline companies.

By **GARRY BARKER**

Airlines around the world are reported to be keeping wary eyes on the Compensation Court of New South Wales where Ms Alyssia Chew, a former flight attendant, is suing Ansett Airlines, claiming fumes leaking into the cabin air-conditioning system damaged her health.

Ms Chew claims that working on the company's "Whisper Jet", the four-engined BAe146, exposed her to fumes that led to her contracting multiple chemical sensitivity and chronic fatigue syndrome.

The hearing before Judge Patrick Moran is now over and a decision is expected in April or May.

Industry observers say up to 3000 pilots and cabin crew with airlines around the world have claimed compensation for long-term damage to their nervous systems.

A report in yesterday's *Sunday Independent* newspaper in London suggests that airlines face lawsuits totalling billions of dollars from employees who say faulty air-conditioning units have caused them loss of consciousness, blurred vision, memory loss and neurological damage.

The paper alleged another Australian airline employee, a woman pilot, claimed to have felt "as drunk as a skunk" on one approach into Brisbane airport when she was in command of a BAe146. The pilot was not named and no date of the incident was given.

Ansett's corporate affairs manager, Mr Geoff Lynch, said yesterday that the company had "done a great deal of work on the BAe146, in conjunction with the Flight Attendants Association of Australia and various other bodies, including several external medical experts.

"There is an overwhelming body of evidence to suggest that no link can be made between the cabin fumes and any long-term health effect," Mr Lynch said.

However, "we are aware that there have been instances of stinging eyes and headaches on a short-term basis," he said.

"We have not ruled out any link between short-term symptoms and possible cabin fumes. But we are very confident that there is no link between cabin fumes and long-term effects."

Mr Lynch said the airline had done an enormous amount of work over the past couple of years on the aircraft engines and seals to make sure oil did not vaporise and escape into the cabin by way of the air conditioning system.

"We are confident we have done as much as we can possibly do with the aircraft, and are very comfortable that what we have done is ensure there is nothing toxic in the cabin that could lead to long-term effects."

Complaints about fumes leaking into airliner cabins go back at least 15 years and mostly have to do with the practice of using engine heat to warm air being pumped into aircraft air-conditioning systems. Allegations have been made that faulty seals allow vaporised oil to leak into the system and be carried into the cabin.

The *Sunday Independent* report says documents tabled in the Chew case show that 14 reports of "strong smells" detected inside BAe146 aircraft had been received by Ansett in less than a year.

The Australian Bureau of Air Safety was also reported to be investigating a separate incident in which a pilot became faint while approaching Melbourne Airport. The aircraft was later found to have a faulty engine seal, the *Sunday Independent* report said.

Figure 0-4: Diagnosis of Chronic Fatigue Syndrome

1. Clinically evaluate cases of chronic fatigue by:
   a. History and physical examination;
   b. Examination of mental status (identified abnormalities require appropriate psychiatric, psychological or neurological examination);
   c. Tests -
      i. standard screening tests;
      ii. additional tests as clinically indicated to exclude other diagnoses.

Exclude if another cause for chronic fatigue is found

2. Classify as Chronic Fatigue Syndrome

I. Classify as chronic fatigue syndrome if both a and b criteria are met:
   a. Unexplained persistent or relapsing fatigue of new or definite onset that is not due to ongoing exertion, is not relieved by rest, and results in a substantial reduction in previous levels of activity;
   b. Four or more of the following symptoms are concurrently present for six months or longer-
      1. impaired memory or concentration severe enough to reduce levels of occupational, social or personal activities,
      2. sore throat,
      3. tender cervical or axillary lymph nodes,
      4. muscle pain,
      5. multijoint pain without joint swelling or tenderness,
      6. new headaches,
      7. unrefreshing sleep,
      8. post exertion malaise lasting more than 24 hours.

II. Classify as idiopathic chronic fatigue syndrome if fatigue severity or symptom criteria for chronic fatigue syndrome are not met.

Controversy remains about the possible physiological, biochemical, immunological, psychological and social aspects of the condition, and possibly all five are important to varying degrees in individual chronic fatigue syndrome sufferers.

Research studies have confirmed that the majority of patients with the chronic fatigue syndrome:

- are white middle-aged women,
- have a high prevalence of current major depression and somatisation disorder,
- have abnormal personality traits,
- believe that their fatigue has a physical cause, and
- show mild abnormalities of humoral immunity.

Contradictory data have been presented with regard to:

- the time of onset of depressive disorders,
- the etiologic role of herpetic and enteroviral infections (post-viral CFS) or chemical sensitivity (chemically related CFS),
- the presence of abnormal cellular immunity, and
- the clinical utility of immunoglobulin therapy.

As presently defined, the chronic fatigue syndrome has many of the clinical and biological features associated with depressive and somatoform disorders. A specific ætiological role for infections or immune dysfunction has not been confirmed.

Psychological and immunological factors both appear to contribute to chronic fatigue syndrome (CFS). By comparing CFS with other disorders in which fatigue is a prominent symptom, the asso- ▶

ciation between fatigue, psychological vulnerability, depression, and immune function can be further defined. The 1988 definition of CFS by the Centers for Disease Control encompasses several conditions in which the major characteristic is severe fatigue associated with constitutional symptoms. Several studies have identified immune dysfunction in CFS patients, but the specificity of these findings remains unclear. Most studies have shown that CFS patients, compared with other patients with chronic medical illness, experience more disabling fatigue. Some investigators have found a higher incidence of concurrent and past psychiatric illness in CFS patients compared with other medical patients, thereby suggesting an underlying psychopathology in CFS. However, other studies have not found a higher than expected incidence of past depression in CFS patients and have further shown that many CFS patients have no identifiable psychopathology. CFS appears to be a heterogeneous entity. Although there may be a high coincidence of major depression in CFS, a substantial proportion of patients lack any identifiable psychiatric disorder yet still manifest the syndrome, thereby suggesting it has an autonomous entity. Recent data from psychological, neurological, and immunological studies that address these issues indicate that despite the evolving nature of our current understanding of CFS, a rational diagnostic and therapeutic approach to CFS is possible.

Chemically Related Chronic Fatigue Syndrome

As noted above, some of the features of multiple chemical sensitivity have similarities with chronic fatigue syndrome, such as fatigue and depression. Labelling of a set of symptoms, such as chronic fatigue syndrome or multiple chemical sensitivity is one way to get recognition that they are medical conditions. However, it is also possible to consider that where chemical exposure is concerned, these particular syndromes are at two ends of a continuum of disease.

The chemically exposed individual with debilitating fatigue may not meet all the diagnostic criteria of CFS or MCS. In some cases, they may be closer to one than the other.

Chemically related CFS is an controversial and slowly emerging medical condition, in which sufferers appear to show fairly similar characteristics:[14]

I a long period of low level exposure to chemicals, such as organic chemicals (for example solvents) but also other materials (for example carbon monoxide and photocopier chemicals);

II a tangible lack of control of workplace chemical hazards (and often indifference) by employers;

III rapid or progressive mental deterioration which may result from either -

A. a "trigger" factor, such as one or more high level exposures, or a significant exposure incident, or

B. prolonged exposure to known neurotoxicants such as carbon disulphide, lead, mercury or manganese.

These precipitate a number of chemical related health effects:

I development of a hypersensitivity or idiosyncratic response to subsequent exposures;

II residual non-specific health effects. A huge range of signs and symptoms have been reported. These include:-

A. headaches,
B. depression,
C. sleeplessness and sleep disruption,
D. night sweats,
E. mental fatigue,
F. personality, mood and affectivity changes,
G. mouth ulcers and sore throat,
H. joint pain,
I. irritability,
J. panic,
K. nausea and vomiting,
L. poor concentration,
M. cognitive impairment,
N. loss of memory,
O. physical exhaustion,
P. inability to tolerate extremes of heat, light (photophobia) or noise,
Q. neurovegetative lability,
R. ocular symptoms,
S. food intolerance,
T. sensitivity to some drugs and chemicals;

Some of these subjective signs and symptoms may have objective measures associated with them -

- skeletal muscle-related symptoms of fatigue and myalgia,
- abnormality of neuromuscular function with increased "jitter" on single fibre EMG studies,
- impaired attention, memory and stimulus evaluation,
- disruption in mitochondrial metabolism,
- mild central adrenal insufficiency secondary to either a deficiency of the arousal-producing neuropeptide CRH or some other central stimulus to the pituitary-adrenal axis,
- immune activation,
- altered cytokine release in peripheral blood mononuclear cell cultures,
- vestibular system abnormalities/disequilibrium.

However, pathophysiological mechanisms of CFS remain obscure;

- the severity of these symptoms vary from day to day and possibly hour to hour, and can last for long periods of time (perhaps even years). Sufferers are prone to relapse if they exceed the limits of physical or mental exertion which their illness imposes.
- removal from risk should, in principle, lead to recovery. However, neurotic stresses may be added to the cause to prolong it indefinitely. These may be seen in the form of pithiatic symptoms (pains and inexplicable impotence) and depressive or querulous behaviour.

Specialists, such as neurologists, endocrinologists, rheumatologists, respiratory physicians, immunologists and so on, are involved with the care of many people with chronic and recurrent fatigue; however, they have not perhaps focused enough research effort on the investigation of fatigue and its management.

Multiple Chemical Sensitivity

Like CFS, MCS is a real disease. The now well accepted name multiple chemical sensitivity was established in the late 1980s, when the first articles on MCS were published. Until that time, there was a lack of a clear definition as to what MCS was, as several medical specialities squabbled about whether MCS is a medical condition, and if so, how it could be diagnosed. Some of the more divisive infighting has been between the allergists and immunologists on one side and the clini-

cal ecologists on the other. This controversy made it difficult for patients to find objective information about the issue, and impeded their ability to resolve MCS-related problems at the workplace, insurance or litigation levels.

"Disease" can be a pathologic process, and not all persons with a disease are ill. Symptoms of illness associated with a disease may be manifest or persist after the disease has disappeared. Many factors, including personal characteristics and social circumstances, can be responsible for recovery from disease and illness.[15] There are many different neurological and psychiatric syndromes that follow acute illness, but their clinical pictures and pathogenesis are poorly understood.

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

The numbers of cases of people with such a chemical sensitivity continues to grow, and the term Multiple Chemical Sensitivity (MCS) has been used to describe this condition.[16] Although this name is now the most often cited, this condition has been known by a variety of names such as environmental illness, hypersensitivity syndrome, twentieth century disease, total allergy syndrome, ecological illness and chemical sensitivity problem.

Diagnosis of MCS

Conditions in which physical symptoms are unsupported by physical findings and have diagnostic labels that describe the disorder without indicating either cause or pathology are especially troubling for the medical practitioner. However, a working definition for MCS was established in 1987.[17] This definition, subsequently modified, suggested a grouping of effects in workers who had been exposed to low levels of several chemicals. A Symposium on MCS was held by the Association of Occupational and Environmental Clinics (AOEC) in the USA in 1991 which proposed a "research definition" for MCS for the purposes of epidemiological study:[18]

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

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

Symptoms of MCS

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

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

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

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

It is quite common in cases of this nature for a patient to be seen by a number of doctors and specialists, some of who are dismissive or unhelpful. However, those medical practitioners who are able to see beyond the limited confines of their own fields of speciality can sometimes see more than a sick liver or a dysfunctional nervous system to see a person who needs help. Such doctors can usually provide some help to the chemically sensitive person, often providing a range of advice, including the exposure basis of the condition, likely prognosis, and recommendations for recovery or level of incapacity.

Different types of chemical sensitive individuals

There are four main types who contain individuals in which heightened reactivity to chemical exposures has been reported (see Table 1, from[19]). ▶

Table 0-1: Chemically Sensitive Groups

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

Exposures that precipitate symptoms of MCS

Initially, individuals respond to one sort of chemical exposure, but if the spreading or broadening phenomenon occurs, the affected individual may respond to a much wider range of chemicals, and the exposures that precipitate symptoms become lower and lower. Table 2 shows a wide range of exposures that have been reported to provoke such symptoms in the chemically sensitive individual.

Table 0-2: Chemical Exposures Implicated in Chemically Sensitive Individuals[20]

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

Chronic Fatigue in MCS

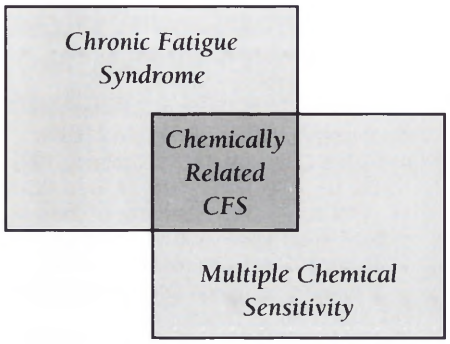
Chronic fatigue is a common outcome, but that debilitating fatigue and a number of associated symptoms following a viral infection for periods greater than six months has been given the name post viral chronic fatigue syndrome. Similar types of symptoms (but with more symptoms and probably less fatigue) may also be reported by people exposed to chemicals. Fatigue, and chronic fatigue, is often part of multiple chemical sensitivity.

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

The chemically exposed individual with debilitating fatigue may not meet all the diagnostic criteria of chronic fatigue syndrome or multiple chemical sensitivity. In some cases, they may be closer to one

than the other. This makes diagnosis (see Figure 5) and treatment problematic.

Figure 0-5: The Relationship of Chronic Fatigue Syndrome and Multiple Chemical Sensitivity



However, chemically related chronic fatigue, that is the presence of fatigue and other symptoms following chemical exposure, sits between these two descriptions.

The Phenomenon of "spreading"

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

Phases of MCS

There are three distinct phases of MCS:

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

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

Investigations into the basis of MCS

The basis of MCS is still to be identified, although a range of hypersensitivity, immunological, psychological, neurological and toxicological mechanisms have been suggested (see Table 3, based on[21,22,23])

Table 0-3: Possible Mechanisms for Multiple Chemical Sensitivity

Mechanism	Comment
Allergic	Most allergic reactions have underlying immune mechanisms that have correlates which can be measured clinically. These correlates are rarely found altered (or only mildly altered) in MCS sufferers, suggesting that MCS is not mediated through allergic mechanisms.
Autosuggestion	Belief that disease (and its causes) exist may be the cause of symptoms. Further, such a belief is perpetuated and reinforced by support groups, medical advisers and the media. Unlikely possible cause as many MCS sufferers must make massive lifestyle changes against pre-existing belief systems.
Cacosomia	Altered olfactory sensitivity. The smell of chemicals may produce autonomic arousal, which becomes amplified with time. Also may be seen as odour mediated panic attacks.
Conditioned response	This theory suggests that smelling the chemical causes a behavioural response which produces the symptoms. However, the reverse in usually the case - most MCS sufferers recognise symptoms first and then find they have been exposed.
Immunological	Immunological Changes in immunological measures are sometimes found in MCS sufferers, but these are often not clinically significant and are not consistent in all MCS sufferers. The changes are also sometimes linked to post viral episodes, such as viral infections.
Impairment of biochemical pathways involved in energy production	Suggests that the fatigue seen in MCS (and CFS) sufferers may be due to impairment of basal energy metabolism in all cells. Those body systems with high energy demands (such as muscles and the nervous system) are affected first.
Limbic kindling	The limbic system is part of the deeper structures of the central nervous system, known to be associated with some of the more stronger emotions. Low level stimuli which do not initially produce a response and which eventually produce strong responses could be mediated through increasing activity in the limbic system. A theory that may explain the multi-organ nature of MCS, and time dependent increases in sensitivity.
Psychosomatic condition	Suggest that symptoms are of psychological origin. Unlikely as most symptoms are related to the conventional toxicity of the chemicals, but at a much lower concentration.
Malingering	Symptoms of MCS are produced so that sufferers can get out of work or to receive compensation. Most unlikely - the range of symptoms between sufferers is too consistent to be based on random symptoms used by many individuals for the purposive avoidance of work.

Mechanism	Comment
Neurogenic inflammation (in upper respiratory tract infection)	It is known that respiratory tract infections produce biochemicals (such as cytokines and messenger peptides) which can cause sensitisation of nervous cells located in the respiratory system. Suggests a possible mechanism of site specific nervous system sensitisation.
Overload of biotransformation pathways (also linked with free radical production)	The functional reserves in biotransformation capacity varies from individual to individual. If this reserve is close to saturation or if it is depleted, the body cannot deal with further toxic exposures. Most MCS sufferers have some disruption in biotransfomation processes (although not usually observed using the crude measures used clinically, for example, in liver disease). Also supports concepts of increasing sensitivity to lower concentrations and increasing numbers of chemicals.
Psychological illness	Suggests that MCS is produced as a by-product of misdiagnosed psychological disease. The possibility of psychological disease should be excluded in diagnosis of MCS. Further, most MCS sufferers undergoing psychological evaluation do not show psychological disease.
Sensitisation of the neurological system	"Neurogenic switching" occurs where a stimulus at one site can produce a reaction at another site.

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

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

Research into the possible mechanisms of MCS is far from complete. However, a number of promising avenues of investigation indicate that the possibility of alteration of the sensitivity of nervous system cells (neurogenic inflammation, limbic kindling, cacosomia, neurogenic switching) may be a possible mechanism for MCS.

Further, many of the other suggested mechanisms, still suggest a chemically mediated trigger in the development or production of MCS symptoms.

Conclusions

There are an increasing number of people showing unspecific symptoms related to low level occupational (or sometimes environmental) chemical stress. A range of models has been proposed to explain these phenomena, including the immunological, neuropsychological, toxicological and sociological models. None work adequately in isolation, and the medical or scientific explanation of polysymptomalogy is yet to be established, although working definitions, and a diagnostic label (Multiple Chemical Sensitivity) has been defined.

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

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Notes

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