Journal of Nutritional & Environmental Medicine (2000) 10, 39–84

BSAENM REPORT

Multiple Chemical Sensitivity: Recognition and Management. A document on the health effects of everyday chemical exposures and their implications

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ISSN 1359-0847 print/ISSN 1364-6907 online/00/010039-46 © BSAENM

EXECUTIVE SUMMARY

1. There has been an enormous increase in the production and use of synthetic chemicals and in exposure to pollutants this century, which has accelerated in the last 50 years. Five million different chemicals are now recognized and relatively few of the chemicals in use have been adequately tested for toxicity to man or the environment. Of the 3000 or so in large-scale use, the 'minimal' toxicity data required by the Organization for Economic Co-operation and Development (OECD) for a preliminary assessment of health hazards to humans are not publicly available for 75%. There has been little study of exposure to combinations of different chemicals, either simultaneously or in sequence.
2. Establishing the *chronic* effects of any exposure is very difficult, even in experimental animals. In humans who are regularly exposed to chemical cocktails that vary from day to day and year to year, it becomes almost impossible unless the outcome is a very rare and well-documented condition. However, it is equally impossible to establish that such exposures are without risk.
3. Long-term ill effects have been reported from chronic exposure to heavy metals and by a minority of individuals after the exposure of defined populations to synthetic or pollutant chemicals—chemical accidents, pesticide exposure, 'sick' buildings, implants, etc. Most of these individuals report that their late symptoms are exacerbated by ambient exposures to volatile organic chemicals (VOCs) emitted by everyday products (for instance, perfumes, washing powders and cigarette smoke), which were previously tolerated without trouble and indeed often enjoyed. Similar chronic conditions occurring in other individuals, after single toxic or sub-toxic exposures, or prolonged low-dose exposure, tend to be overlooked. This condition is referred to as multiple chemical sensitivity (MCS).
4. The genuine nature of MCS has been recognized by officially commissioned reports from independent scientists in the USA and the UK, who have concluded that it is a valid diagnosis and a sometimes disabling condition, although all have stressed the need for further research.
5. Because of their biological roles, it has been suggested that pesticides (designed to interfere with enzymes) and hormone mimics may have a particular place in inducing MCS. However, the evidence also implicates VOCs and other compounds such as diesel particulates and the nitrogen oxides.
6. A large study in Bristol has found associations of air freshener and aerosol use with increased prevalence of certain symptoms in both mothers and babies.
7. Patients with MCS are often treated as if their symptoms are psychologically caused. There is no good evidence for this. On the other hand, double-blind challenges have provided positive evidence for the provocation of symptoms by certain chemicals (varying in different patients) at levels too low to be recognized by the patient; challenge has been reported to cause changes in brain activity on SPECT scans.
8. These patients are usually found, on investigation, to be suffering also from the effects of 'hidden' allergy (intolerance) to a number of different foods and food additives. The symptom reactions they experience are often dissociated in time from the ingestion of the trigger food in such a way that the connection has not previously been made. A number of clinical conditions (*see below*) appear to be specifically associated with this loss of tolerance to foods and chemicals, and with increased susceptibility to biological airborne allergens (pollens, mould spores, animal danders, etc.).
9. When low-dose chemical exposure is frequent or constant, the link between exposure and symptom development may be obscured by a dissociation in time similar to that seen in hidden food allergy and the connection may not have been recognized.
10. If exposure continues, the degree of sensitivity may increase and the range of troublesome substances (both xenobiotic and natural) may increase. At this stage

patients are often placed on a number of different drug therapies to control their symptoms. Reactions can also extend to encompass reactions to these drugs. If, however, enough of the incitants can be identified and exposure to them avoided, some reversal may occur, with re-establishment of tolerance to at least some of the exposures.

11. The use of the word sensitivity in the name multiple chemical sensitivity describes the observation that, after initiation of the syndrome (but not before), patients are adversely affected by low concentrations of some chemicals and chemical mixtures, well below those considered to be possibly toxic; these concentrations do not appear to affect other people. The patients have become *sensitized* to them. The mechanisms underlying MCS have not been established, but some characteristics are reminiscent of immunological phenomena.
12. MCS forms part of the recently described *toxicant-induced loss of tolerance (TILT)*, in which potent, repeated or combined stressors—chemical, physical, biological and psychological—provoke a loss of tolerance to environmental factors and foods, leading to a wide array of chronic illness, including a number of conditions with established labels. It has been predicted that TILT will ultimately be recognized to be as important to the understanding of disease causation in our day as the germ theory of disease has proved to be.
13. The increase in allergic disease in the last 50 years has been described as epidemic, but the increase actually dates from early in the industrial revolution when hay fever was first reported. Although the increase in allergies has been attributed to changing patterns of infection, gut flora and immunizations, the correlation with industrialization both in the UK and world wide makes it likely that the increase in exposure to synthetic and pollutant chemicals makes a substantial contribution. There have been comparable increases in prevalence of the other conditions which are becoming recognized as being due to loss of tolerance, such as irritable bowel syndrome, migraine, Crohn's disease, serous otitis media and attention deficit hyperactivity disorder. The data do not yet indicate whether the reported association of earache and diarrhoea in infants with the use of air fresheners is a sign of an influence of chemical exposure on the prevalence of allergic diseases in general, or merely a local effect.
14. Patients with MCS need help, both from society in making it easier for them to avoid VOC exposure and from the medical profession in the recognition of the disorder and in its management.
15. Members of the British Society for Allergy, Environmental and Nutritional Medicine (BSAENM), and colleagues overseas, are consulted by such patients every day. Although more effective treatments are needed, the methods that are currently in use help many of the patients to identify causal incitants, to reduce exposure to them, and to become less sensitive, although this may take a long time. This is demonstrated by some of the illustrative cases in the Appendix. The BSAENM regrets that the only environmentally controlled unit in the UK, an essential facility for the treatment of severe MCS, has recently had to close because of a hiatus in the funding of referred patients.
16. Initiation of chemical sensitivity follows higher dose exposure or repeated or prolonged exposures: in sensitized patients symptoms are provoked by very low concentrations. As a society we should be attempting to reduce exposures of the population in general to synthetic and pollutant chemicals (whether inhaled, ingested or absorbed through the skin) so that fewer individuals become sensitized; preventing the provocation of symptoms in sensitized individuals requires much more stringent control of exposure.
17. There is an urgent need for teaching about chemical sensitivity to be included in the medical school curriculum and in postgraduate schemes of study so that it is more reliably recognized and better managed. Such teaching requires the recruitment to medical schools of academic staff expert in this area; this is unlikely to be possible for all medical schools until it becomes easier to obtain funds for this type of research.

18. Since it is impossible to prove that chemicals are entirely safe (and we see daily evidence to the contrary), the precautionary principle should be invoked and active measures be put in hand to reduce exposure to chemical compounds to which the general public has wide exposure, whether the compounds have been shown to be hazardous or not. Particular attention should be paid to reducing exposure to pesticides, persistent organic pollutants, VOCs (including artificial fragrances), synthetic food additives, and pollutants from smoking, chemical manufacturing, power stations, and traffic. It is particularly urgent to cut down exposures during development (*in utero*, infancy and childhood) when the risks are highest, and to prevent the young from accumulating persistent organic pollutants before they have their children.

1. INTRODUCTION

We live in a chemical world and all human metabolism is chemical in nature. However, for the purposes of this document the term *chemical* will be used to describe chemicals which do not contribute to normal metabolism—mainly man-made synthesized chemical compounds and chemical pollutants. These may be termed *xenobiotic*. Some compounds in this category appear to be non-toxic, some are very toxic, others cause toxicity only at higher exposures or only in compromised individuals. Toxic effects may be acute or chronic. In keeping with the terminology of toxicology, the term *toxin* will be used to refer to natural substances, *toxicant* to synthetic chemicals.

However, this document, the third in our series [1,2], is not primarily concerned with toxicology although there will be areas of overlap. Xenobiotic chemicals have been reported to cause adverse effects in a minority of individuals at doses much lower than the lowest that has been shown to be toxic and it is these effects referred to as multiple chemical sensitivity (MCS) [3–6], that are the main focus of this report. Independent scientists in the USA [7] and the UK [8] have concluded that, although there is still much to learn, it can no longer be doubted that MCS is a genuine complaint. There are indications that MCS may be, at least partly, allergic in mechanism although not IgE-mediated [9]; the symptoms provoked are similar to those seen in 'hidden' food allergy. The term *chemical sensitivity* is a term describing the acquisition of a state of enhanced sensitivity in which symptoms are provoked by exposures to very low concentrations of chemicals that previously had no effect [4,10]. It does not pre-empt the decision about the mechanism.

Classical toxicology has been concerned with acute and chronic reactions to individual compounds (not usually examining interactions between chemicals) and has sought to establish threshold doses for toxic effects for each chemical below which it has been assumed that the product is without danger to people. However, effects of a range of familiar chemicals on the brain at subtoxic doses are beginning to be detected which are likely to cause a rethink [11]. Chronic or delayed effects of exposure are notoriously difficult to detect and attribute, even in experimental animals. This is even more difficult if only a subpopulation is involved, or if the effect occurs only with exposures to multiple compounds. Humans are now subjected to a mixture of chemical substances that change, not only from person to person, but also from day to day and from year to year, some of which accumulate in the body. Some evidence suggests that responses to foreign substances entering the body may not follow traditionally-accepted dose-response curves; low levels of mixtures of xenobiotic chemicals may actually be more damaging than higher levels because they do not trigger the induction of appropriate detoxification enzymes [12]. The full ramifications of the effects of the multiple chemicals to which humans are exposed have not been established but the chronic effects on which this report focuses are in addition to the recognized risks from carcinogenicity and mutagenicity; chemical exposures may also increase susceptibility to other aetiological agents, and in particular to the development of allergic disease.

This report will focus on the evidence that adverse reactions occur consistently in a

minority of individuals at exposures below the traditionally recognized toxic threshold, and will consider the clinical features and management of such conditions. In some of these cases there is a history of a single toxic exposure but in others the increased susceptibility seems to follow long-term exposure or exposure to multiple chemicals which may all be present at doses below the toxic threshold. The report will examine the extent of the problem, and evidence for the hypothesis that chemical exposures have contributed to the marked increase in the prevalence of allergies and related diseases in the last 200 years, especially in the last 50 years.

These are relatively new fields of medical interest. They are neither classical toxicology nor standard allergy, but should be of concern not only to epidemiologists but also to clinicians. In the past, the medical profession has found sporadic cases of MCS difficult to recognize and accept, but this is beginning to change since chemical sensitivity has been recognized in a minority of individuals when groups have been exposed, for instance in work-related exposure incidents [13,14] or in new or refurbished buildings (so-called sick building syndrome; *see later*). Such incidents have been reported from the USA, Canada, the UK and most other countries in Europe.

A major reason for the emphasis on chemical sensitivity in this report is that this important area of human responsiveness has lacked an academic discipline to represent it; those concerned with occupational health tend to think only of exposures at work. Physicians who have developed the skills to detect environmental reactions among their patients recognize these phenomena on an almost daily basis although, as yet, it has remained largely unacknowledged in the UK. This is likely to change as a result of the independent report commissioned by the UK Health and Safety Executive [8], and by the recent European Union (EU) document [15]. The only previous UK scientific report on this problem, from the campaigning group Friends of the Earth [16], is written solely from the viewpoint of toxicology.

Chemical sensitivity presents regulatory problems to governments and employers with regard to exposure and use, restriction of trade and the provision of safe alternatives. The topic has been considered in a number of symposia and workshops in the USA [17–21].

2. THE SCALE OF CHEMICAL CONTAMINATION

Alone among animals, humans have been able to cause substantial and intentional modifications to the environment. This began with the introduction of metal smelting some 10 000 years ago and the pace has increased dramatically since the industrial revolution. Some hydrocarbons, such as coal, have been burnt since the 13th century [22] but demand increased with population growth and industrialization in the 19th century. The 20th century has seen the exploitation of liquid hydrocarbons and natural gas to such an extent that many reserves have been used up. Considerable quantities of combustion products are released into the air as a result: an estimate for 1992 included 3500 kilo tonnes of sulphur dioxide, 2750 kilo tonnes of nitrogen oxides, 6708 kilo tonnes of carbon monoxide and 2556 kilo tonnes of VOCs.

The chemical industry hardly existed at the start of the 19th century but is now a world-wide major producer. The UK chemical industry has annual sales totalling £33 billion and it was calculated that in 1997 the average family spent £25 on synthetic chemical products each week [23].

Sixty to seventy thousand synthetic chemicals are now in regular use. Production in the USA increased by 1200% from 1945 to 1985, when 107 million tons year^{-1} were made [7,24]. More than 5 million different compounds are now recognized. Chlorine production grew from less than a billion tons year^{-1} before 1939 to 163 billion tons year^{-1} in 1976 [7]; it is regarded as an index of the production of synthetic organics. Many of these compounds are now in domestic use [25]. In the UK in 1992 2.1 million tons of plastics were produced, an 11% increase in 5 years [26]. Over 200 000 tons of additives are added

each year to our food [27]; over 3000 chemicals are added, most of which are xenobiotics. By 1982 75% of the average diet was found to be processed food [28]. Traditional perfumes are made from natural musks, spices and flower extracts but the majority are now synthesized, and are added to many everyday products, including detergents, polishes and toiletries. Almost none of these synthetic aromatic cosmetic products appears to have been tested for toxicological effects on humans.

Commercial chemical fertilizer production went up from about 2 million tons world wide in 1950 to about 49.4 million tons [29] by 1983. Prior to 1945 most pesticides used in the UK were either natural compounds (pyrethrum, derris) or inorganic materials such as arsenicals. UK production of synthetic pesticides increased by over 700% from 1948 to 1982, with over 500 different products being marketed; more recent products have greater potency [30]. By 1988 pesticides, mainly herbicides, were applied to 97% of all arable crops, involving 22.4 million kg of active ingredients [31]. Organic solvents are used as carriers for most sprayed pesticides.

Pharmaceuticals (mainly xenobiotic chemicals) dispensed through NHS chemists have increased from 240 million items in 1949 to 440 million in 1989 with a large increase in the proportion due to synthesized drugs [32]. Silicones, as implants and injections, have been in use since the Second World War. Over a million women in the USA are estimated to have had silicone breast implants [33]: in the UK about 8000 such implants take place each year. Silicones have also been employed in orthopaedics in joint replacements (especially the temporo-mandibular joint and following skull trauma) as replacement testicles and cosmetically in false chins [34]. They are now being used in replacement lenses following cataract surgery [35]. Depot preparations of contraceptive hormones (Norplant) use silicones as a vehicle [36].

It would be possible to add to this list, but this is enough to show that exposure to chemicals has increased massively over the last two centuries. The sheer volume raises doubts about safety; these are not allayed by the limited availability of toxicity data. It has been stated that for 75% of the 3000 or so chemicals in large-scale use the 'minimal' toxicity data required by the OECD for a preliminary assessment of health hazards to humans are not publicly available [37]. A report commissioned by the State of New Jersey [7] found that no toxicity data, or only minimal data, existed for 66% of pesticides and their supposedly inert ingredients, 84% of cosmetic ingredients, 64% of drugs, 81% of food additives and 88–90% of commercial chemicals. Exposure to large numbers of different chemicals raises further questions about possible toxicity since very few interactions between chemicals have been looked for and some unexpected ones found [38,39]. At our present rate of progress it could take several hundred years to catch up with adequate testing of the chemicals currently used, even if no new ones were to be introduced.

When these chemical compounds are used in industry, at home or in foods and medicines they give rise to contaminated waste products, many of which find their way into watercourses, either directly or indirectly. Attempts to clean up the industrial and agricultural contamination of rivers are beginning to be effective, but little attention has so far been given to contamination due to the excretion of medications and their metabolites. Testing rivers and drinking water for the large numbers of drugs and metabolites would be a very extensive commitment. However, some of these compounds are likely to be biologically active at lower concentrations than some industrial compounds since, like pesticides, they were developed for their biological activity.

3. IS THERE AN UNRECOGNIZED PROBLEM?

a) General

Acute exposure to toxic chemicals, and severe effects of chronic exposure, are usually limited to a small exposed population in commercial or industrial settings and subject to

strict controls [40]. However, the marked increases in the combustion of fuels and in the use of synthetic chemicals for all sorts of purposes have given rise to much greater exposure of the general public. Air pollution has been associated with increased demands on casualty services, exacerbation of asthma [41] and higher mortality [42]. A large community-based study in China found an association of preterm births with periods of higher air pollution, maximal after a 7–8 day lag period [43]: preterm birth is associated with poorer subsequent health and is the most important cause of perinatal mortality in developed countries.

Some exposures to chemicals in the domestic situation may reach toxic levels: for example, the concentration of pesticide in houses recently treated with pesticides was reported to be substantially above the industrially acceptable upper limits [31]. In most other non-industrial instances each chemical is present at levels far below those regarded as toxic, and a lack of adverse effect is assumed. However, the large number of products in use militates against the identification of sub-acute or chronic effects of any one of them, and against the detection of harmful interactions between chemicals. The question therefore arises as to whether present chemical exposures do cause medical problems in the general population, and if so, how common they are and how serious.

We shall try to address this question as far as we can, quoting health problems for which an apparently causal link to chemical exposures has been demonstrated but is not generally recognized. However, it is our perception that these discrete instances represent only a small part of the overall problem: in many others there is clinical and anecdotal evidence linking ill health to everyday chemical exposures. It is not possible at the present time to distinguish in all instances between the effects of increased individual susceptibility to *toxic* effects of chronic exposure and the state of *sensitization*, whatever that may prove to be; the two may ultimately prove to be closely linked. There is an urgent need for research, but it is notoriously difficult to establish firm links between any exposures (or other factors) and chronic or delayed effects, as the work on the role of smoking and dietary factors in coronary heart disease (CHD) has shown. Adverse effects limited to a sub-group of the exposed population are unlikely to be recognized unless they are acute, or cause a rare condition such as asbestos-induced mesothelioma. However, it is even more difficult, in fact virtually impossible, to prove that chemical exposures do *not* cause chronic ill health, except in a population that is completely healthy.

When the safety of chemicals is assessed, thresholds are derived below which it is commonly assumed there is no risk, based usually on an assumption that humans could be up to ten times more susceptible than another species. The possible effect of sensitization is usually considered only if there is clear evidence in animals of IgE-mediated allergy, or if the chemical structure suggests the likelihood of contact sensitization. Yet MacPhail reports that chemical sensitivity can be induced in laboratory rats, where the range of sensitivity among individuals may span orders of magnitude [44], and other evidence suggests that responses to chemicals may not always follow traditionally accepted dose-response curves [11].

Susceptibility to toxic effects in humans varies for a number of reasons [45]. Susceptibility is greater during rapid development, in the presence of some enzyme anomalies, and in the presence of deficiencies of key nutrients. Some individuals are genetically more susceptible than others. Risks are greatest to the foetus and child [46,47] and many chemical contaminants are transferred from mother to the foetus [48] or infant [49]; even minor set-backs to development can cause lifelong susceptibility to a range of diseases [50]. Vitamins and metallo-enzymes are needed for the breakdown and detoxification of xenobiotic chemicals (*see later*) and are therefore utilized in greater quantities as exposure increases. Vitamin deficiencies are increasingly being recognized; they were noted in about 30% of supposedly healthy individuals in two population studies, more common in women [51,52], and may influence the outcome of pregnancy [53]. There is a study showing decreasing selenium levels [54] in the population but none about other essential trace elements; however, deficiencies of zinc and magnesium are also common in patients with

MCS and 70% of a series of 158 patients referred to a hospital environmental allergy clinic showed zinc deficiency [55]. If any of these essential nutrients are in short supply, excretion may be impaired, growth, repair and immune system function adversely affected (even if only marginally) and the body more at risk from the toxic and teratogenic effects of even small exposures, as demonstrated by the thalidomide story [56,57]. No teratogenic effects were reported when routine toxicity tests of thalidomide were performed in well-fed animals; after teratogenicity had been noted in humans, it was demonstrated in animals fed on diets deficient in any of a number of key nutrients [56,57]. Chemical exposures contribute to the induction of other congenital abnormalities [58,59] and, as early as the 1930s, Price found that abnormalities of the development of the facial sinuses were common in developed countries but entirely absent in isolated communities [60].

b) Medications

Much of contemporary medicine depends on the use of pharmaceutical drugs as a primary response to ill health. The majority of these prescriptions do not cure, but are merely palliative [61]. Initial testing of pharmaceuticals can be, and often is, supplemented by data collected during use, relating to larger numbers of subjects; tighter controls often ensue, pointing to the inadequacy of the initial assessment, in spite of the enormous costs involved. Many drugs are licensed only for adults, not because they are known to cause adverse effects in children but because they have not been tested, although doctors are at liberty to use them, at their own discretion. None of the systemic preparations listed in the Data Sheet Compendium is without adverse reactions and side effects [62]. About 4% of prescriptions have been reported to cause significant side effects and 0.1% to be fatal [63]. In the USA, 10% of hospital admissions over the age of 65 were for medication toxicity [64]. There may be cross-reactions between drugs and environmental chemicals but none has been documented to our knowledge, although food/drug interactions have been reported. Some side effects of drugs are undoubtedly allergic in mechanism. Reactions to medications may not be to the active principle but to fillers, preservatives or dyes [65]. Clinically we see reactions that appear to be provoked by traces of chemicals used in manufacture and supposedly removed.

c) Implants

Recently there have been suggestions that the materials of implants, especially (but not only) silicone, may cause illness; most of the data comes from breast implants but some also from the use of silicone in replacement lenses [35] and facial reconstruction [66]. Although licensed for implants, silicone is not licensed for administration by injection because it is known to cause local effects—microembolism, granulomata, skin atrophy and local inflammatory responses [67]. Breast implants consist of a silicone bag enclosing a solid matrix with 55–95% liquid silicone to create a soft consistency. The bag acts as a semi-permeable membrane through which liquid silicone may pass out by diffusion, a phenomenon known as ‘gel bleed’. This starts to occur in all implants as soon as they are manufactured and continues after implantation. Leakage of silicone is accelerated when the implants rupture: their rupture rate is estimated to be 50% by 12 years and 95% by 20 years [68]. It has been recommended that all implants should be replaced after 7 years [68]. The silicone bags are relatively radio-opaque (interfering with mammography screening) and cause microcalcification, a radiological lesion typical of malignancy. In one silicone bag which was subjected to analysis, the detection of 8 elements was reported—platinum, chromium, silver, nickel, vanadium, barium, copper and cobalt. These were all present in the gel and the ‘shell’ [69].

Gel bleeds deposit silicone in the same physiological space as silicone by injection, and

cause the formation of a pseudo-capsule of scar tissue which may be up to 2 cm in thickness: histopathology shows silicone droplets, silicone granulomas, chronic inflammation and fibrosis [70]. There may be local hardening, pain and tenderness as it contracts on the incompressible implant. Treatment is often by 'closed capsulotomy' where the breast is crushed between the surgeon's hands to rupture the scar capsule, but may, and often does, also rupture the implant, allowing increased silicone dispersal [71].

Silicone migrates to distant sites. In experimental animals, silicone was found in fat, the gastrointestinal tract, liver and spleen after intraperitoneal injection [72], spread occurring by transport by macrophages after phagocytosis and by microemboli [73]. Pfleiderer found that 36% of 125 women with implants had silicone detectable in the liver [74]. There is no known mode of excretion. Susceptible individuals show immunological reactions to silicone and the anti-polymer antibody levels correlated with symptom severity [75]; some of the pathological lesions are probably mediated by delayed hypersensitivity.

Systemic symptoms are characterized by chronic fatigue, and by autoimmune conditions (including thyroid disease, rheumatoid arthritis, scleroderma, SLE, Raynaud's disease, sicca syndrome) [76] and neuropathic disorders such as polyneuropathy and central demyelination [77].

d) Mercury

Chronic heavy metal poisoning primarily affects low-turnover tissues, especially brain, fat, breasts, testes, ovaries, bone and kidneys. The risks from lead, cadmium, and aluminium are well recognized, and overload with iron is a clinical problem; these will not be considered further here except to note that the potential implications of low-level long-term exposure to heavy metals are enormous, because the exposure starts in intrauterine life since there is no placental barrier to toxic metal transfer. Few studies have been concerned with the degree of damage inflicted on the developing brain by such early exposures.

The role of mercury is less well recognized. Mercury is both toxic and capable of sensitizing; clinically the two mechanisms may be difficult to distinguish. In the 19th century its toxicity was recognized from its use in the treatment of syphilis and in industry. It was a well-known cause of dementia, illustrated by the mad hatter in Lewis Carrol's *Alice in Wonderland*. Toxic effects of high doses include tremor, delirium, hallucinations and suicidal tendencies. If inhaled, mercury may cause chest pains, breathlessness, coughing and haemoptysis, and if ingested, gastroenteritis. In skin lightening creams it can lead to nephrotic syndrome [78]. Mercury from polluted fish provoked an epidemic of acute tubular necrosis of the kidney in Minimata, Japan; it is still found in fish from polluted waters.

Toxic effects of low but continuous doses are less obvious but there is evidence of low level toxicity; as with lead, it is probable that there is no safe dose [79]. The average daily intake from food has been estimated at 3.09 μg (of which three quarters, 2.2 μg, is absorbed) [80,81], but its greatest use recently has been in amalgam fillings [82], introduced 150 years ago.

Estimates of absorption from amalgam vary from 1.2 μg daily to 100 μg, with an average of about 10 μg [83]. Fillings are made up from a 1:1 mixture of mercury with an alloy of silver 70%, tin 25%, and small amounts of copper and zinc. Dental health is improving but there are few adults with no amalgam in their mouths. At room temperature mercury is liquid and very volatile; seven fillings give off about 10 μg mercury vapour metre^{-3} exhaled air; after chewing or hot drinks vapourizing roughly doubles [84,85]. When radioactive mercury was used to put fillings in the teeth of sheep, radioactivity was found in the lungs, liver, bone and gastrointestinal tract, and was very high in the kidneys and the frontal lobes of the brain; it also appeared at high levels in the foetus and breast milk [86].

Mercury competes with selenium for binding sites on the enzyme glutathione peroxidase which has a protective role in the detoxification of some harmful peroxides. Experiments in mice showed that tissue levels of vitamins B1, B2, B6, and E all decreased during

intoxication with methyl mercury chloride [87]. Like cadmium and lead, mercury appears to interfere with the active transport of vitamin B12 across the blood–brain barrier: the brains of 10 patients with Alzheimer's disease had consistently high levels of mercury and low levels of selenium and zinc [88].

Mercury is an occupational hazard for dentists [89] and some evidence of neuropsychological dysfunction has been found in 90% of American dentists [90]. The fertility rate of dental nurses was only 63% of that in a group of women not occupationally exposed to mercury [91].

Healthy people may seem to be tolerating amalgam fillings with no detectable adverse effects but minor toxicity may increase vulnerability to other environmental insults and cause insidious effects on vital tissues such as the immune system and the brain. Susceptibility varies between individuals, possibly due to genetic factors such as HLA groups, or to previous exposures to other xenobiotics, infections or stress. Nanogram doses of mercury have provoked inhibition of granulocyte [92] and lymphocyte function [93]. Sensitization to mercury occurs in some patients and may be related to the development of symptoms. In 1969 three groups, each of 60 patients with no occupational exposures, were patch tested; those with no amalgam fillings had no positive patch tests; of the individuals with amalgam fillings, patch tests were positive in 8.3% of the healthy individuals but in 26% of the allergic group [94].

Removal of amalgam fillings should not be undertaken lightly, and can make patients worse (particularly in the short term), but there is anecdotal evidence of relief of symptoms in many patients [95]. Now that there are so many alternatives, the continued use of amalgam is hard to defend.

e) Pesticides and Related Compounds

Pesticides are a particular concern since they are designed to disrupt the enzyme systems of the target species, and related compounds are hormonal mimics. The similarity of all animal biochemistry means that human (or other animal) contamination with such products must always contain an element of risk, difficult to quantify at low exposures.

DDT and other organochlorines (OCs) were widely used for decades until the extent of bioaccumulation was documented; Lindane is still used in the UK and others elsewhere; OCs are still in the environment and bioaccumulation continues. There are now extensive data incriminating delayed toxicity reactions from OCs [96–100] and other compounds [101–103], a study indicating that exposure may be a factor in breast cancer in women [104], and others linking them with Parkinson's disease [105–107].

Polychlorinated biphenyls (PCBs) have been associated with infertility and miscarriages [108,109]. Growth deficits were present at birth in the children of mothers who had been eating contaminated fish from the Great Lakes in the USA and memory deficits were found at 4 years of age [102,103], both showing linear correlations with PCB exposure before birth. The high levels of OCs in the fish in the Inuits' diet, and the resulting contamination of their breast milk [110], have led to them being advised not to breastfeed their babies, depriving those babies of other, protective, factors.

Evidence that pollution can cause horrendous health problems in humans, particularly when combined with inadequate nutrition, comes from the heavily polluted Aral Basin [59] in Central Asia. Pesticides in water samples were found to be 30 to 70 times higher than the EEC upper limit of safety, with high pollution of crops from polluted water sources and wind-blown pollutants. The rates for ischaemic heart disease (23–30% in women), thyroid disease and cancer were very high, with gastric and oesophageal cancer representing 30% of new cancer diagnoses; over 90% of ostensibly healthy adults had clear evidence of gastritis on gastroscopy. There is an extremely high rate of genetic abnormalities—at least 14.5% of pregnancies end in spontaneous abortions, 4.2% of live births are premature with

57% showing developmental abnormalities—and high infant mortality. Russian literature is said to include other documented effects of pesticides including hypertension, chronic hepatitis, mental retardation and psychiatric illness, and detectable changes in a number of immune parameters [59].

Organophosphates (OPs) were introduced to farming as the long-lasting environmental effects of OCs became clear. Initially much more stringent precautions were recommended for handling the OP concentrates than for dipping, but these have been gradually increased for the latter by the addition of gloves, visors and aprons, and now by what is virtually a chemical warfare suit [111]. Long-term low level exposure has been linked with neuropsychological effects [112–114], even at dosage levels below those known to cause cholinesterase inhibition. Chronic symptoms in these farmers are worsened by exposure to minute amounts of pesticide, but often also by exposures to other chemicals, and some foods, as is shown in Case 5 (Appendix 1). The report by the Royal College of Physicians accepted the reality of the condition and concluded that 'existing clinical services for patients with symptoms associated with OP sheep dip exposure are unsatisfactory' [115], and called for research, but had nothing new to suggest.

There are also reports linking minor exposures with carcinogenesis in children [116]. These effects may be of vital importance as an organophosphorus compound is now being assessed as a prescription medicine [117,118]. Organophosphates are reported to have adverse effects on micronutrient status [119,120]: if substantiated this could be of wide significance because nutrient failure can contribute to, or worsen, a variety of apparently unrelated complaints. Patients with a history of symptoms from OP exposure had lower bone formation at tissue and cellular level than unexposed controls [121].

Accidental exposure to pesticide spray has appeared to be the event initiating loss of tolerance as, for instance, in the case described in the Appendix to reference 97.

f) Gulf War Syndrome

Veterans of the Gulf War, both from the USA [122–124] and from the UK [125–127], have suffered more ill health than would have been expected, which they attributed to their service in this campaign. The rate of ill health was especially significant considering that the group were young and with a bias towards good health since, for service, their fitness had to be classified A1 [124]. The causal factor(s) must have been environmental. The servicemen and women involved were not aware of similar problems in colleagues without Gulf War service and the problem was presented as being a new illness. Unfortunately the veterans' complaints were not taken seriously at first in either country and were not investigated by the military medical services or by government. When it was recognized that there was a significant cohort of illness in these subjects the problems were attributed to psychological causes.

Recent papers have reported clinical and epidemiological studies of UK servicemen. They show that those who served in the Gulf were about three times more likely to have become ill than non-deployed service personnel and at least twice as likely to be ill as those who served in Bosnia [125], but that there was no unique pattern of illness. The patients suffered from multiple symptoms and the main diagnostic headings recognized by the authors [125,127] were chronic fatigue, post-traumatic stress reaction or the CDC-multisymptom syndrome [122]. The authors concluded that the data provided firm evidence that service in the Gulf War affected the health of servicemen and reported a correlation between the syndrome and the special Gulf War immunizations, and exposure (or belief in exposure) to chemical weapons. Unfortunately they gave no details about the results of analyses of other exposures, such as personal pesticides, the OP sprays used extensively in living accommodation, diesel exhaust fumes, oil well fires [125] or these exposures in combination. The data showed a lower, but still surprisingly high, prevalence of multiple symptoms in servicemen who had not gone to the Gulf but had served in Bosnia or at home.

The authors did not comment on the fact that the proportions of servicemen who had used personal pesticides or pesticides on their bedding or clothing were in roughly the same ratios in the three populations as those with symptoms, or show analyses to exclude pesticide exposure as a provoking factor. The service personnel complained of symptoms similar to those which occur in OP exposed farmers [112] and in patients with MCS [3–6,128]. Some of the USA veterans showed focal cortical abnormalities on SPECT scan similar to those in patients with MCS [129]. Preliminary investigations support the diagnosis of MCS [130], and the progress of the few servicemen with Gulf War syndrome treated on this basis has supported that diagnosis. This diagnosis was accepted by a recent consensus document [131].

The two British papers [125,126], co-authored by a representative of the US military medical services, show evidence of meticulous thought in their programmes and interpretation. We therefore find it astonishing that, while possible psychological causes received detailed scrutiny (of 10 authors of the first paper at least 4 have psychiatric affiliations), so little evaluation was performed on the chemical exposures of these servicemen in spite of extensive coverage in the US literature, which must have been available to the authors [122–124]. Now that it has been established that the Gulf War caused illness among the servicemen involved, a detailed evaluation of the possible causes should be performed, taking seriously the possibility that chemical exposures contributed to the initiation of this illness. There is now experimental evidence to show that a combination of non-toxic doses of the chemical treatments given to the servicemen and women serving in the Gulf could be neurotoxic. Simultaneous treatment of hens with any two of the anti-nerve agent pyridostigmine, DEET (an insect repellant) and permethrin (an insecticide) caused significant neurotoxicity and fatalities, most severe in the group given all three, although the doses used were not toxic, or showed minimal toxicity, when given singly [39]. However, neurotoxicity may not account for all the servicemen's symptoms and for many the diagnosis of MCS [128] is the most appropriate. This was supported by a pilot telephone survey of US Gulf veterans [130].

g) Sick Building Syndrome

There have been a number of incidents reported from the USA [132], Canada [133,134], the UK [135] and most other countries in Europe, of what has been called Sick (or Tight) Building Syndrome. Occasional instances have been due to microbiological [136] or mould contamination, usually of the ventilation system, but most were in new or newly refurbished buildings and were attributed to environmental chemicals, mainly VOCs. The condition has occurred mainly in newer buildings with a heating, ventilating and air conditioning plant (HVAC) within a sealed structure. Such systems recycle the air with a modest rate of extraction and replacement with fresh air. VOCs are generated by the structure itself, by the fittings and furnishings, cleaning materials and from the clothing, perfumes and smoking of the occupants, and from the activities undertaken in the building [134]. Synthetic fabrics, and residual dry cleaning, detergent and fabric conditioner volatiles from clothing make a substantial contribution.

One of the incidents occurred after the USA Environmental Protection Agency (EPA) building was refurbished in 1987–8, using 27 000 square yards of new carpet [132]. About 2000 people worked in the building, of whom 124 became ill and 2 left; 17 could not subsequently work in their assigned spaces even when the levels of VOCs had decreased. This was attributed to the use of 4-phenylcyclohexene to bind the carpet to the backing: 5–15 parts per billion (ppb) seemed to have been sufficient to sensitize, but sensitized individuals subsequently reacted to 1 ppb. In another incident, sick building syndrome affected many of the staff of three hospitals in Halifax, Nova Scotia, which were contaminated by chemicals distributed from a common heating plant [133]. In the wake of

these developments a Government-sponsored pilot clinic in environmental medicine was converted to a full-time service at Dalhousie University School of Medicine [134].

Sick building syndrome is avoidable [132,137]. One of our members was consulted after the first of two new buildings proved to be a 'sick building'. He was part of a team which advised on the investigation of the building and the remedies required: there were no microbiological findings which could have contributed to the outbreak, but VOCs were detected, including toluene, n-propyl and ethyl benzene, trichloroethane, vinyl chloride, formaldehyde and di-isocyanates [138]. The concentration of VOCs correlated with instances of reported ill health. The recommended remedial work was successful and eventually the affected workers were able to continue to work there, symptom-free or with symptoms they considered insignificant. The team also advised on the completion and commissioning of the second building, ensuring that sources of VOCs were kept to a minimum and that the ventilation system had a sufficient intake of fresh air: this also was successful. About 1000 people were employed in each of these buildings; in the first building 28 people considered themselves to have been affected by the building and to have been ill enough to volunteer for medical investigations. Problems included dry skin, rashes, headache, tiredness, nasal discharge and blockage—a number also had episodes of collapse (*see Appendix 1, Case 4*). In the second building only one minor case of illness was reported [138].

Indoor pollution with VOCs is not limited to the workplace [9,139–141]. It has increased in homes as more synthetic materials are used and with attempts to save fuel by stopping draughts [142]; similar medical problems exist in ill-ventilated homes [143]. However, these mainly affect women (since they tend to spend longer in the home) and are usually attributed to premenstrual syndrome or the menopause, or to psychological causes to which women are believed to be more susceptible. Our members see such cases frequently and in most cases symptoms improve markedly when the usage of perfumed household products and toiletries is reduced, ventilation increased and/or gas appliances are switched off (*see Appendix 1, Case 1*).

The reports of investigations of sick building syndrome underestimate the importance of formaldehyde in 'sick' buildings since, in a number of cases, the investigations employed did not appear to estimate formaldehyde. Clinically, the formaldehyde released from building materials, synthetic fabrics and fabric treatments is an important incitant in patients with MCS (*see Appendix 1, Case 3*).

h) Volatile Organic Chemical Concentrations and Late Symptoms

It is difficult to be sure which exposures might have reached toxic levels at some time in the instances discussed above, but in each case only a proportion of the exposed population developed symptoms, indicating variable susceptibility, even to the initial exposure. After the initial exposure, whether it was to implants, mercury, pesticides, the Gulf War or to a 'Sick' building, a variable but usually small proportion of patients have become sensitized so that very low concentrations of the same and other chemicals subsequently provoked symptoms in a number of different systems; many of the patients also developed hidden food allergy and the symptoms of chronic fatigue syndrome. This is characteristic of the syndrome MCS although in many of the above instances this name has not been applied. When MCS occurs after a group exposure, it is more likely to be recognized (though not always taken seriously); sporadic cases may not be. From the EPA incident [132], it appeared that, for the mixture of VOCs involved, 5–15 ppb were required to provoke sensitization after which 1 ppb was sufficient to provoke symptoms in the sensitized. In practice one would hope that, if levels of exposure can be regularly kept below 5 ppb (or the equivalent threshold for other mixtures), the lower levels may be well tolerated. Sensitivity will be induced in some people exposed at the higher level, so that subsequently even levels of 1 ppb or below cause them symptoms. One study concluded that poor quality

indoor air with raised VOC levels had been responsible for initiation of MCS in at least 63% of patients [12].

The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) [144] found increased prevalence of symptoms in both mothers and infants in homes where air fresheners or aerosols were used, based on reports on over 8000 babies and 9000 mothers. There were significant associations of air freshener use with infant diarrhoea and earache, and mothers' depression and headache/migraine, and of aerosol use with infant diarrhoea and mothers' headache. In a sub-group the exposure reports were validated by exposing Tenax tubes for twelve consecutive months to estimate total VOCs. The highest and lowest concentrations of total VOCs detected from individual samples were 11.4 mg m^{-3} (from a living room) and 0.02 mg m^{-3} (from a main bedroom) and the highest and lowest geometric mean concentrations from the twelve samples from the living room of any house were 1.559 and 0.063 mg m^{-3}. There were significant differences between homes.

i) The Prevalence of Multiple Chemical Sensitivity

There have been no studies of the prevalence of MCS in the UK, but studies in the USA have revealed surprisingly high figures. In three population studies [7,145–147] and two workplace studies [148,149] subjects were asked whether they considered themselves to be especially sensitive to some chemicals and between 15.9% and 34% answered affirmatively. Most of these successfully avoided the chemicals in question and were not ill. In three studies totalling over 5000 people, between 3.9% and 6.3% said that they had been told by a doctor that they had chemical intolerance. These studies were done in different states, some of which have few environmental doctors [7].

The highest estimate (34%) was from a telephone survey of 1027 adults in a rural population [146] in eastern North Carolina; it may be relevant that one of the highest estimates for the prevalence of *allergies* was also reported from a rural area in China [150], where it seemed to be associated with pesticide use. In the largest study of MCS [147], which reported on 4046 adults, 13 questions were added to a regular telephone survey of a sample of all Californian homes with telephones. Individuals reported sensitivity in reply to three different sets of questions asking about:

- doctor-diagnosed MCS (6.3%)
- unusual sensitivity 'to everyday chemicals like those in household cleaning supplies, paints, perfumes, soaps, garden sprays or things like that' (to any 15.9%, more than one 11.9%, a lot 4%)
- 'very sick' (American usage) from each of 6 exposure scenarios (tobacco smoke 7.6%, others 1.8%)

Unexpectedly, the preponderance of women and higher education/income groups seen among clinic populations with MCS was not evident. As in the North Carolina study [146], questions were angled at inhaled environmental chemicals so that reactions to food additives, food and water contaminants and medications may not have been retrieved consistently and may account for the imperfect overlap of positive reports.

It may not be totally valid to extrapolate results from California to the UK but, since no UK figures are available, there is no better way of estimating the numbers of people likely to be involved. Applying the results of the Californian study [147] to the numbers of adults in the UK would give figures of over 3 million with physician-diagnosed MCS, nearly 8 million people regarding themselves as unusually sensitive to chemicals (2 million to a lot of chemicals), and over one and a half million with a 'health problem or impairment that restricts … ability to do ordinary daily activities such as bathing, shopping and working' not necessarily due to chemical sensitivity. There is no reason to believe that substantially fewer individuals in the UK would be affected by low-level chemical exposures than in the US but, given the different degrees of awareness in the two countries, diagnosis by physicians

in the UK is likely to be less common and fewer patients may have been alerted to the problems.

4. SITES POTENTIALLY INVOLVED IN REACTIONS TO CHEMICALS

Theoretically xenobiotics may cause damage:

- acutely at the port of entry or in other susceptible tissues
- by accumulation in a tissue
- by cumulative damage to a biochemical or structural component, localized or widespread
- by sudden release from a storage site e.g. sudden weight loss with mobilization of chemicals stored in fat
- on transfer to the foetus
- after metabolic conversion to a metabolite, either toxic (e.g. paracetomol) or to which the patient is sensitized [151,152]
- by inducing deficiency of an essential nutrient
- by increasing the tendency of the host to generate harmful responses, including allergic responses, to other substances, not necessarily toxins in their own right i.e. an adjuvant effect
- by secondary effects due to blocking of enzyme systems

Toxic accumulation of chemicals poses risks [153] that are difficult either to establish or exclude except when the accumulations can be measured, for instance in fat, as is the case for some of the pesticides and related compounds [154]. Subtoxic exposures to xenobiotic chemicals could cause symptoms in patients with nutrient deficiency, or enzyme deficiency of other origin, or perhaps from bioaccumulation. However, consistently repeated symptoms from exposure to doses that are several orders of magnitude lower than those that are toxic are more likely to have some other mechanism.

5. POSSIBLE MECHANISMS INVOLVED IN MULTIPLE CHEMICAL SENSITIVITY

There is currently no consensus about the mechanisms that underlie MCS, except that toxicity, in the usual sense, does not explain the phenomenon. In occupational medicine it is recognized that some ill-effects of chemicals at low concentrations are caused by allergic mechanisms [10]. A few chemicals have been shown to act as allergens or haptens in classical responses [155–157], some mediated by an IgE mechanism (for instance toluene diisocyanate [155]), others perhaps not [158]; many other chemicals cause contact sensitivity [159]. A recent report details a case in which anaphylaxis was caused by hair dye [160]. Some side effects of medications are undoubtedly allergic in mechanism [65,161], and others at least employ the same final pathways.

In clinical practice it is clear that adverse responses to low-dose chemical exposures frequently occur in patients with hidden food allergy and/or allergic reactions to biological airborne allergens. Prevalences of nasal allergy, asthma, urticaria, multiple food sensitivities, irritable bowel syndrome, migraine, sinusitis and arthritis were each more than twice as high among those who reported that they were ‘especially sensitive to some chemicals’ in a population study; all were statistically significant, the allergic diseases very highly so [145]. Moreover, in MCS the reactions to chemicals show some of the characteristics of allergic reactions, and the possibility that at least some of the symptomatology attributed to very low dose chemical exposure has an allergic mechanism is therefore worthy of serious consideration. Such responses

- are acquired
- are provoked by exposures which do not affect most people

- are acquired
- are provoked by exposures which do not affect most people
- are consistent on retest
- are specific to that substance
- are relieved or substantially reduced by prolonged avoidance
- seem to respond to specific desensitization procedures
- may not be recognizably associated with the chemical incitant until after a period of avoidance, especially if there has been frequent or constant exposure; this is similar to hidden food allergy

It has been suggested that the clinical data could be accounted for by recognizing two differing patterns of 'allergic' response, which have been called Type A and Type B allergy [1,9] to draw attention both to the characteristics they share and to the ways in which they differ. The two types may, and often do, coexist. Recognized allergic phenomena are designated Type A. Type B reactions are a distinct, more chronic, class of reaction for which allergic mechanisms have not been conclusively established, although they remain the most satisfactory explanation. Type B allergy rarely (if ever) causes life-threatening reactions, but a wide range of chronic or recurrent symptoms respond to methods of management based on the hypothesis that they are caused by Type B allergic mechanisms. These involve a wide variety of systems, often provoked by foods or biological airborne allergens.

Some academically orientated immunologists do not accept Type B responses as *allergic* and limit *allergic diagnoses* to cases in which specific IgE antibody can be demonstrated, and cases with contact sensitivity. This, however, ignores Types II and III of the four classic immunological mechanisms causing tissue damage [162] and limits Type IV to local reactions occurring in the skin only. The possibility that these types of immune reactions have wider pathological and aetiological significance is gaining wider credence.

In clinical practice MCS seems to be part of the wider condition which Miller refers to as *toxicant induced loss of tolerance* (TILT) [128,163] in that, as well as showing adverse effects from low dose exposures to chemicals, many patients also have sensitivities to foods and other environmental factors: symptoms resolve when the incitants are avoided.

Miller introduced the new patho-aetiological concept of TILT to account for this. This proposes that severe or recurrent exposures to stressors—chemical, physical, biological and psychological—result in a loss of tolerance to environmental and food factors, which then provoke symptoms. She points out that the aetiological implications of this concept may well prove to be as far-reaching for our day as the 'germ theory of disease' has proved to be since its introduction in the late 1980s.

A number of publications have set out criteria for the diagnosis of MCS [4], all requiring that the condition is acquired, associated with symptoms which vary with exposure and are provoked by very low concentrations of incitants. Cullen [164] included other restrictions—requirements for reactions to multiple unrelated chemicals and for symptoms not to be explained by any available test of organ dysfunction. A 1999 consensus [131] calls for greater recognition of MCS, basing diagnosis on chronicity, reproducibility of symptoms in response to low levels of exposure to multiple unrelated chemicals, symptoms improving or resolving with avoidance, and also required that symptoms occur in multiple organ systems. In our view, although most affected patients do react to multiple unrelated chemicals with symptoms involving multiple organ systems, these restrictions conflict with biological realities and are inappropriate for clinical diagnosis, although they may be appropriate for trials. It seems particularly illogical to exclude cases in which reactions to chemicals provoke bronchospasm [165] or some other measurable change. But there is also no evidence to suggest that reacting to a low level of exposure to one chemical differs from the characteristic state of MCS except in severity and extent. The 'spreading' phenomenon seems to be an inherent quality of MCS while exposure continues, and patients with limited

reactions may be about to react to other chemicals, or in other body systems; indeed this progression is regularly seen in the case histories of patients with MCS.

We favour the postulates proposed by Miller [7,163] for the patho-aetiological concept of TILT which were as follows:

- When a subject simultaneously avoids all chemical, food, inhalant and drug incitants, remission of symptoms occurs (unmasking).
- A specific constellation of symptoms occurs with reintroduction of a particular incitant.
- Symptoms resolve when the incitant is again avoided.
- With re-exposure to the same incitant, the same constellation of symptoms reoccurs, provided that the challenge is conducted within an appropriate window of time. Clinical observations suggest that an ideal window is 4–7 days following the last exposure to the test incitant.

In our view, diagnosis of MCS should be made, based on these postulates, when one or more of the incitants are synthetic or pollutant chemicals (or mixtures of chemicals) at low concentration, although it might be more correct to apply the term *chemical sensitivity* to the apparently monosensitive. As pointed out by Miller [163], the first postulate may not be met unless the patient is admitted to a clean environment (*see Patient Management section*); the diagnosis cannot be rejected if this has not been tried. In cases which fulfil the postulates unusual sensitivity to chemical exposures is established; the causal mechanism is not.

MCS patients with multiple symptoms are usually regarded as somatizing since standard medical teaching associates multiple symptoms with a psychological aetiology. A number of publications [166–171] have supported this type of aetiology by finding current or prior psychiatric illness in some of those suffering from MCS (but never in all), by concluding that the presence of 'psychological-type' symptoms indicates a psychological aetiology or by noting some degree of relief using various psychological therapies. This view draws support from the fact that the symptoms provoked by chemical incitants in patients with MCS commonly include psychological symptoms [1–4] including panic attacks [172]. However, there is increasing concern about the 'psychologization' of illness [173], about the distress it causes to patients, about its effect on deductions about aetiology, and about the missed diagnosis of a range of underlying pathologies due to false attribution. MCS is a chronic condition and patients who have been ill for years are likely to be depressed and anxious even when the primary pathology is not psychological, and it is not surprising that psychiatric therapies give some relief [166–168]. However, patients with primary psychiatric illness would not be expected to get relief on admission to a clean environment as is regularly observed in patients with MCS [174–176]. Nor would they show consistent symptom provocation on challenges with trigger chemicals [174–176], even when administered double-blind [177]. The demonstration of focal abnormalities in the cortical areas of the brains of chemically sensitive patients on SPECT scans, differing from the changes seen in depression, and accentuated by challenge with sub-odour levels of incitant chemicals [178], also argues for a primary biological and environmental cause of these symptoms, including depression. Several reviewers have concluded that laboratory results in MCS are not consistent with a psychological origin [3,7].

Moreover, there is no conclusive evidence that psychological factors are causal, in spite of claims to the contrary. Davidoff and Fogarty [179] reviewed the ten papers published after 1980 which reported new data on the psychogenic origins of MCS. The reviewers identified 15 possible methodological problems in these studies concerning sample selection procedures, measurement and study design; only one of the ten studies failed on fewer than eight of these. Study design problems were prominent in nine of the papers. The reviewers recognized six possible hypotheses to explain the occurrence of psychogenic symptoms in MCS: in only one of these were psychological mechanisms the principle causal factor. The reviewers stated that *'None of the authors advanced testable cause and effect hypotheses or*

used a study design that could distinguish correlation from causation, yet eight authors considered their data supportive of psychogenic explanations'. Davidoff and Fogarty's conclusions amount to an authoritative rebuttal of the widely held assumption of psychogenic causation of symptoms in MCS and are supported by others who have reviewed the literature [7–9,180]. Some psychologists and psychiatrists go further and state that biological mechanisms must be given more attention generally if the aetiological factors contributing to mental illness are to be unravelled. Rippere has stressed that psychological diagnoses should be positive and not made by exclusion, and put in a plea for separating psychological *causes* of illness from *secondary* psychological phenomena [181]. Jacob [182] has drawn attention to the fact that current diagnostic categories which use symptoms to characterize syndromes have not led to viable explanations of the aetiology of mental disorders, and suggested that subcategorization employing biological variables should be tried.

Chemical exposures may have occurred in stressful situations, and the resulting syndrome is often attributed to stress. Stress is known to affect immune system function adversely [183–187]. It increases the likelihood of sensitization and reduces the stimulus needed to provoke reactions in the sensitized and so may play a part both in the induction and the expression of chemical sensitivity [188]. In a study of older persons, those who had symptoms from chemical odours reported significantly greater stress levels up to 40 years of age but not at the time of the survey [149]. However, the secondary role of stress is shown by the fact that, if the allergic provoking factor can be completely avoided, stress may no longer provoke the symptoms; this is illustrated by a study of migrainous children, many of whose parents reported that migraine was provoked by stress *before* an elimination diet but not when incitant foods and food additives were being *avoided* [189]. Stress may also provoke hyperventilation which has been noted in patients with TILT. These relationships are complex: in our experience hyperventilation may provoke symptoms typical of allergic responses but may also be triggered by them; this may represent the body's attempt to normalize the low tissue pH associated with allergic reactions [190]. The physiological changes caused by hyperventilation cause or exacerbate a variety of symptoms [191]. Interpretation is complicated by the close relationships between immunological and neurological mediators [192], and by the report that histamine release can occur as a learned response [193].

Other hypotheses have been put forward to account for acquired susceptibility to very low dose exposures. Some of these focus on the sense of smell and neural conditioning to odours [194], on neuroinflammatory mechanisms [195], on time dependent sensitization [196] or on shared characteristics with animal models of repeated electrical stimulation causing kindling of the limbic system and eventually seizures [197]. Animal experiments have confirmed that repeated low dose exposure to chemicals can cause sensitization, but the extent to which these hypotheses are capable of explaining the phenomenon of MCS in humans is not yet established [7,21]. Some of these mechanisms appear to be limited to exposure by inhalation or to be derived from an animal model that differs from the human experience. In our opinion, allergic (but not IgE-mediated) mechanisms currently show the best fit with the human data overall.

One unexpected experimental finding which may turn out to have significance for the causal mechanism of MCS requires mention. McLaren Howard has recently done a series of studies on a patient monosensitive to a certain hair spray, who decided to continue to use the hair spray after the link was established, and agreed to be studied repeatedly. On double-blind challenge, the hair spray (but not an indistinguishable placebo provided by the manufacturer) provoked the previously experienced symptoms, and consistent signs, but also several unexpected temporary changes, including an increase in Gamma GT and an increase in serum peaks for Lindane and DDT, 20 min after challenge (*see Appendix 2*). The latter changes were noted on six occasions when challenges with genuine hairspray were given double-blind and did not occur with the placebo. This suggests that some symptoms might be provoked secondarily by the release of toxicants from stores, in

response to a challenge, possibly cytokine-mediated: these possibilities need further investigation.

6. THE RELIEF OF CHRONIC ILLNESS BY METHODS BASED ON THE CONCEPT OF TYPE B ALLERGY

In spite of the availability of potent medicines, the numbers of the population who claim to have chronic illness rose 66% between 1972 and 1996 [198]. There is a high prevalence of 'medically unexplained' symptoms, and conventional medical management of these conditions is, by definition, inadequate [171]. Among 191 and 229 new referrals to general medical outpatient clinics no fewer than 52% and 45% respectively were allotted to this category [199,200], and three-quarters still had symptoms about ten weeks later, in spite of reassurance. TILT may cause conditions with many different medical and surgical diagnoses (including asthma, eczema, rhinitis, attention deficit hyperactivity disorder, irritable bowel syndrome, Crohn's disease, migraine, depression and chronic fatigue) or regarded as 'medically unexplained', as well as many tiresome symptoms which are largely disregarded by the medical profession [1,4,9,176].

Allergic disease is increasing markedly in prevalence [150,201–203]. Insofar as there is data, the same is true of the other conditions caused by TILT [204–206]. At least 20–25% of the population of developed countries are likely to be affected at the present time. When a large number of chronic conditions are managed as if they were due to reactions to environmental factors and foods, relief has been reported in as many as 70% of patients, even when the symptoms have been present for 10 years [9,176,207–211]. Hidden allergy to foods or food additives is usually the predominant intolerance, but many also need to reduce exposures to volatile chemicals to get good symptom relief, and in some cases the symptoms are predominantly due to MCS. Failure to recognize that some form of allergy probably contributes to this group of conditions is currently delaying progress in understanding them and in establishing the mechanisms responsible.

In hidden food allergy, the symptom reactions are often dissociated in time from the ingestion of the trigger food in such a way that the connection has not previously been made. The association of the trigger with the symptom(s) may only be recognized after a period of avoidance of the trigger. Under these circumstances, avoidance initially causes a worsening of symptoms (referred to as withdrawal) which is followed after about a week by a marked improvement; if all the relevant triggers have been avoided even polysymptomatic patients may become symptom-free. Symptoms are subsequently provoked by challenge with certain incitants and not by others. This may only be clearly demonstrated when the challenge is given during the most sensitive period (between 1 week and 4 weeks after avoidance started); after this, symptoms may not follow single meals but recur if repeated consumption is resumed.

Reactions provoked by chemicals may be masked in a similar fashion to foods, especially when exposure is frequent or continuous (*see Appendix 1, Cases 1 and 3*), but the period required for symptoms to clear when exposure is avoided may be longer [175]. Masked reactions to chemicals may interfere, not only with the elucidation of chemical sensitivity, but also with the investigation of hidden food allergy. Hidden allergies to either foods or chemicals cannot therefore be *excluded* unless testing is performed in a clean environment, namely an environmentally controlled inpatient facility (*see Patient Management section*). Withdrawal of all drugs may also be necessary.

The uncertainty about the mechanisms underlying Type B reactions does not negate the clinical observations [1,9] that:

- detection of hidden food allergies and chemical sensitivities is *clinically* beneficial in many patients with chronic and recurrent symptoms
- the patients remain free of the symptoms if they can avoid the incitants

- they develop symptoms when they fail to do so
- if they can avoid most incitants they become well and remain well long term

It would be more satisfying to be certain about the mechanisms involved, but the uncertainties about mechanisms should not influence judgement as to whether the evidence of efficacy is convincing or not. Advances in understanding mechanisms would be welcomed primarily for the stimulus they might bring to refining methods of diagnosis, investigation and management.

7. HAS CHEMICAL EXPOSURE CONTRIBUTED TO THE INCREASED PREVALENCE OF ALLERGIES AND RELATED ILLNESSES?

The prevalence of allergies has increased in the last two centuries; the increase has been most marked over the last 50 years [201]. Several studies have reported a doubling of the prevalence of allergies over as short a period as 10–15 years [201,204]; for instance a study of prick tests to a panel of three allergens in adults (30–65 years) in London found that at least one test was positive in 46% of subjects in 1988 compared with only 23% in 1974, a doubling in 14 years [202]. Prevalence continues to increase [205] and allergies are now affecting nearly half of some industrialized [203] or pesticide-exposed populations [150].

There is circumstantial evidence that chemical exposure may have contributed to this [201], for instance from the epidemiology of hay fever. We now accept this as a common pollen allergy. However, the world's *first* description of it was by Bostock in London in 1819: in the next 9 years he heard of only another 18 cases [212,213]. In Japan the industrial revolution occurred much later and the main seasonal rhinitis in Japan, from cedar pollen, was not noted until 1964 but had been seen earlier in Japanese living in the USA [214]. From 1960 to 1980 the peak pollen counts in London decreased, but the prevalence of hay fever rose from 3% in 1962 to 19.7% in 1981 [215]. Clearly the prevalence of a genuine pollen allergy has been increased by some other environmental factor. In the early years, pollenosis rose in parallel with industrialization and coal burning. More recently, other pollutants including the fine particulates from diesel exhausts have been implicated [201]. A number of pollutants have been shown to act as immunological adjuvants; the adjuvant potential of most other chemicals has not been assessed. Adjuvants increase and modify the response of the immune system to any allergens (or antigens) present at the time. Oily emulsions have been used regularly as experimental immunological adjuvants, and there is experimental evidence about diesel particulates [216,217], nitrogen oxides [218] and some saponins [219]. Enhanced IgE antibody production and a changed pattern of cytokine production in humans followed simultaneous exposure to diesel particulates and ragweed pollen by the nasal route [220].

The increase in asthma tells a similar story [204,205]. Before the Second World War asthma was relatively rare and considered a benign condition with virtually no mortality. Now the annual UK asthma death rate is well over 1000. Increasing numbers of children in the UK need to take inhalers to school with them, rising to over a quarter of children in the worst polluted areas [221]. These changes are affecting the developing world; for instance, asthma was unknown in Xhosa children living in tribal homelands in South Africa, but common among those who had moved to the city [222].

In each of these instances there are two strands; the specific (the pollen, house dust mite or chemical to which the person becomes sensitized) and the background influences which predispose to sensitization. In IgE mediated allergies pollutant chemicals have been shown to contribute to both, and it is likely that they do so in non-IgE mediated reactions too, but other mechanisms may also be involved reflecting other particular biological activities. Some evidence particularly incriminates pesticides (synthesized to interfere with enzyme systems) and compounds which mimic hormones [96], but these alone would not account for the historical data. Clinical experience suggests that the overall load of xenobiotics may influence the outcome. Humans are now exposed to a complex mixture of chemicals, very

few of which have been properly evaluated for their potential harmful effects, interactions, or adjuvant activity; unexpected toxicity was noted when a combination of food additives was tested [38] and more recently has been reported for combinations of pesticides [39] (*see Gulf War Syndrome section*). In mice, the cytogenicity of benzene was increased by administration of a non-cytogenic chemical and decreased by dimethyl sulphoxide (DMSO) [11].

Foreign chemicals which cannot be utilized in human metabolism impose a detoxification burden whether inhaled, ingested or absorbed through the skin. Increasing quantities of vitamins and metalloenzymes are utilized as the load increases (*see section on Nutrition*); deficiencies are increasingly being recognized [51–54]. If these essential nutrients are in short supply, biotransformation and consequently excretion of chemicals is impaired: growth, repair and immune system function may be adversely affected, even if only to a small degree: the body will be more at risk from the toxic and teratogenic effects of even low exposures [56,57]. As in animals [96], risks are greatest to the foetus [223] and to the child during rapid growth [102,103] and compromised development can affect brain development and cause lifelong susceptibility to a range of diseases [50].

Other mechanisms have been put forward to explain the recent increase in allergic disease. These include the changed pattern of infectious disease in infancy, the increased use of antibiotics and consequent changes in gut flora, and the changes in immunization patterns. Any or all of them may be contributing but this does not invalidate the observations about the role of chemical exposure.

8. PEOPLE AT RISK

The concept of *biodiversity* was established many years ago and is now supported by evidence of a wide range of differences in the biochemical make-up of genetic and environmental origin [224]. The bodily build of, for instance, the Inuit people and the Somalis are very different and provide an adaptation to the circumstances in which they live. Within a more coherent group, such as the population of the UK, inbuilt adaptive mechanisms are less obvious. Changes arise over many generations and the current chemical exposures have been too recent for any substantial genetic modifications to have evolved. Resilience in the face of exposure is therefore mostly by chance rather than by design.

While some subjects apparently cope with current chemical exposure levels, others are more vulnerable and fall chronically ill from levels tolerated by the majority: the reason for this vulnerability to MCS needs to be identified. If MCS is allergic in nature, it may be that all allergic individuals are at risk, currently approaching half the population of industrialized countries [201–203]. However, in reported incidents the proportion of exposed individuals reporting MCS has been considerably less than this and some other factor or factors (for instance micronutrient deficiencies) may be needed as well.

The onset may follow an exposure to a single substance (usually a toxicant), sometimes, but not always, at a level causing acute toxic effects. In other subjects a similar exposure may cause no effect or only an acute illness followed by complete recovery, but in the minority who develop MCS it induces sensitivity which may extend to cover a wide range of chemicals and often foods and biological airborne allergens as well. The initial exposure seems to be an *initiating phenomenon* and does not necessarily feature strongly in the subsequent sensitivity spectrum, although it may do so.

Not all MCS patients have a history of atopic allergy, and from the practical viewpoint of setting environmental exposure limits for susceptible individuals such a history would be unhelpful in view of the prevalence of a history of allergy [201–203]. At our present level of knowledge about MCS the only practical solution would seem to be to keep exposures for everyone below levels which have been shown to initiate sensitivity in susceptible individuals. Overlap between MCS, sick building syndrome,

chronic fatigue syndrome and reactive airways (both lower and upper airways) has been noted.

9. DIAGNOSIS

a) General

The term MCS is appropriate for affected patients who have become intolerant of a number of different chemicals: there are, however, other patients with similar but usually less severe illness, who are affected by only one or two chemical incitants; chemical sensitivity is the more accurate term for these, but the diagnosis should be established in the same way. Some illustrative case histories will be found in Appendix 1.

At the present time diagnosis of MCS is made by a combination of history, observation and challenge studies, since no conclusive laboratory tests have been available. Tests which show the disruption of enzyme activity support the diagnosis of chronic toxicity, and the presence of IgE antibody specific for the chemical (free or as a hapten) an atopic mechanism. As in all other investigations, negative findings are only valid as far as they go. Failing to find disruption of one enzyme system does not exclude disruption of others, and an absence of IgE antibody does not exclude other immunological reactions. At the present time, however, there is no laboratory test that covers the other forms of hypersensitivity and is suitable for routine clinical use. Even patch tests require interpretation to distinguish irritant from immunological reactions [159].

The basic characteristic of MCS patients is that they may become, and remain, reasonably well if they can avoid exposure to the chemicals and other incitants to which they are sensitive. Studies which report immunological, biochemical and other investigations are only relevant if they compare symptomatic MCS patients with individuals with *no* symptoms (acute, chronic or intermittent), or compare baseline findings after days of avoidance (for which an environmentally controlled unit may be required [225]; *see Section on Research Priorities*) with those after challenge with the chemical and with placebos (as in the investigation detailed in Appendix 2).

Up to the present time diagnosis has had to be a clinical matter. The definitive diagnosis is reached by challenge studies and confirmed by subsequent progress. However, a London laboratory is developing quantitative tests of lymphocyte sensitization to a range of xenobiotic chemicals at the single cell level; initial results are very encouraging [226].

b) The History

The history may suggest MCS if symptoms started after an event associated with an increase in chemical exposure, sometimes after a long interval. Common examples include a house move to a new or recently refurbished house, a job move (either to more polluted premises or involving more exposure to traffic pollution), or accidental exposure to the use of pesticides or other chemicals (spraying, or dry or wet rot treatments or fumigation for infestations, for example). Sometimes decorating at home or at work, exposure to new carpets or furniture, or the use of different toiletries or cleaning compounds may initiate symptoms. In some cases there appears to have been no immediate change in chemical exposure but there has been prolonged or severe stress, an operation or a long course of medication, or an illness which seemed to be viral.

Unless the initiating event is explicitly toxic, symptoms will only be noted *after* the induction phase. The patient may have linked the change in exposure with the development of symptoms, but has often not done so. A careful history often elicits the fact that the patient now avoids entering shops which sell perfume, or the washing powder aisles in the supermarket, or dress shops, or shops selling a lot of plastic goods, because they make them feel unwell. They may have stopped wearing perfume even if they have always liked it.

Because of the exposures involved, patients may have difficulty in going into crowded places such as trains and buses, churches, theatres or cinemas, or going on car journeys.

The patient may present with any of a wide range of symptoms. The symptoms are often vague but disabling, and of varying severity. Many patients complain of feeling unwell, often described as feeling 'lousy', and may suffer from fatigue similar to that in chronic fatigue syndrome. Neurological and cognitive impairments are more common in response to chemical incitants than to standard allergens or inciting foods. Brain fag (tiring quickly) or brain fog (reversible difficulty with cognitive tasks) are common, but patients may also suffer from unreasonable behaviour, panic attacks, sensory disturbances or changes in muscle tone or co-ordination. After some chemical exposures a few MCS patients get episodes of disturbed consciousness, or even collapse (*see Appendix 1, Case 4*). Such disturbances have been reproduced under strict challenge conditions. It seems likely that patients who present with reactive neurological symptoms or collapse provoked by specific environmental exposures are commonly misdiagnosed as hysterics.

A wide range of other symptoms may also be provoked in these patients, similar to those suffered by other patients with Type B allergy [176], including reactions such as bronchospasm which can be measured [9,165,227].

c) Challenge

Patch testing is employed routinely by dermatologists in reactive skin complaints using a number of different batteries of chemicals determined by the history, and is also used by environmental allergists, mainly to test toiletries and cleaning products in patients with dermatitis [159]. Some of the chemicals routinely used for patch tests may give positive results when sensitive patients are challenged by other routes.

Ingestion challenges may be used for food additives and oral medications. Otherwise, challenge with low doses of chemicals and chemical mixtures may be performed in one of three ways [9,174]:

- by dropping a saline dilution of that chemical or mixture under the tongue
- by intradermal injection
- by inhaled exposure at low concentration in a specially constructed booth

If symptoms are consistently provoked by challenge with chemical extracts at very low doses, unrecognizable by the patient and administered in a blinded fashion, but not by exposures to placebos, this is good evidence for chemical sensitivity. It is particularly strong when confounding influences are excluded, the reaction is measurable and consistent on repeat, when the reaction is observed by experienced professionals, and when long-term avoidance of that substance is subsequently associated with improvement.

Avoidance prior to challenge is best effected by admission to an environmentally controlled unit, but lesser measures, such as turning off the gas supply, moving into a less polluted house (or one with different pollution) or into a tent, or being tested directly after a holiday, have proved effective. Cases 1 and 3 (Appendix 1) provide examples.

d) Outcome

The diagnosis may be confirmed by the patient's subsequent progress—by the patient's ability to keep well, or at least substantially better, while avoiding the triggers identified, and subsequent development of symptoms on exposure, whether the patient is aware of the exposure or not.

10. PATIENT MANAGEMENT

There are a number of techniques that are used to reduce the frequency and severity of the symptoms of chemical sensitivity, but it can be an intractable problem and the difficulties it causes can rarely be overcome completely. The core of the management approach is avoidance of provoking allergens, foods and chemicals, the provision of clean air, food and water, and optimizing the patient's nutritional state to enhance detoxification. Research is needed to establish the effectiveness of the methods in use and ways of improving delivery, and to develop other techniques (*see section on Research Priorities*).

The following methods are currently employed:

- Techniques to minimize exposure
  - Avoidance
- Techniques to enhance excretion
  - Nutrition
  - Sauna detoxification
  - Chelation therapies
- Techniques to reduce the severity of the effects
  - Nutrition
  - Low-dose desensitization
  - Psychological therapies

a) Avoidance

Whatever the mechanisms or the characteristics of an individual's chemical problems, once the diagnosis has been established the first and most obvious measure is avoidance or reduction of exposure. Given the ubiquitous spread of synthetic and pollutant chemicals, total avoidance may well be impracticable. Nonetheless there is good evidence that simple changes aimed at reducing the chemical burden can be beneficial [9,12]; for example, a survey of 305 MCS patients [228] found that 93% reported that avoidance measures helped them significantly. Two studies commissioned by the Canadian Government clearly demonstrated the benefits of moving to cleaner surroundings for patients with chemical sensitivity [229,230].

There are a number of precautions that can be useful in reducing exposure. Patients should be particularly advised to:

- avoid exposure to levels of any toxicant high enough to initiate MCS. [Patients should, for instance, be warned not to expose themselves to new furniture, paint, and carpets, and to fumigations]
- avoid ongoing low-level exposures to toxicants to which they are already sensitized and ensure that their house is well ventilated to prevent build-up of VOCs originating indoors

Indoor air quality presents both a major problem in this respect and a major opportunity. Home environments are often a source of sensitization through heavy exposures, for instance to the fumes from gloss paint, or the adhesives and bonding agents in new carpets [14,132,231]. Removing such chemicals from the home environment as far as possible and increasing ventilation is an obvious first step towards avoidance. Workplace environments have been well documented as being capable of triggering chemical-related problems [12,13], and simple practical measures to minimize exposure can reduce or even reverse symptoms.

External airborne pollution is, of course, less avoidable, and if individual sufferers find that basic measures such as improving in-house and in-car air filtration and air quality, or altering routes and means of travelling to work are insufficient, then relocation to a less polluted environment may be necessary.

b) Nutrition

The principal route of elimination of the majority of xenobiotic chemicals from the body is by detoxification in the liver, secretion in the bile and final excretion in the faeces. Detoxification in the liver, the major organ of detoxification (although comparable but less understood processes take place in the skin, lungs and gastrointestinal mucosa), is performed by the hepatic microsomal enzymes. There are two stages to the process; both are capable of being overloaded, and both are dependent on there being an adequate supply of the nutrient substrates and co-factors involved in what are high-nutrient-consuming enzyme reactions [232,233]. The enzymes involved in Phase I, which are referred to jointly as cytochrome P450, prepare the molecules of toxin for the second stage. Phase II of detoxification involves conjugation, the joining of another compound to the toxin to make it unreactive and therefore safe. Compounds used in Phase II include sulphate, glutathione and sulphur-containing amino acids, and a lack of any of these can adversely affect the detoxification process [234,235].

Laboratory investigations can demonstrate changes in a number of such variables—induction (increased activity) or failure of the relevant enzymes, reduced reserves of substrate, deficiencies of specific nutrients—that may lead to impairment of detoxification and consequent overload in other areas of biochemical activity. There is evidence that MCS sufferers are more likely to be deficient in such nutrients [236]. Furthermore, nutritional supplementation appears to be able to increase detoxification activity by as much as 40% in healthy adults [237]. It has been shown that this can lead to clinical improvement in a number of conditions, including Gilbert's disease [238], as well as in MCS [239].

Sulphur amino acids play a role in the conjugation of xenobiotic chemicals for excretion via the bile, for which omega 6 essential fatty acids and vitamin C are said to be co-factors, reducing reabsorption in the gut [240]. There are therefore theoretical reasons for including these supplements in the regimes of patients with chemical problems.

c) Sauna Detoxification

Although the liver is the major organ of detoxification, with the products excreted in the bile and urine, the skin (in sweat and sebum), the breath, and breast milk represent secondary excretion routes. Several different regimens have been introduced designed to stimulate the excretion of xenobiotics with a combination of exercise, heat from saunas and nutritional supplementation. Patients are required to exercise (in order to increase blood flow), undergo massage (to mobilize fat deposits and the toxins they contain), to take high doses of niacin, vitamin B3 (to provoke cutaneous flushing), and to spend time in a sauna (to raise body temperature and increase sweating) [241–243]. This is conducted on a daily basis for approximately 3–4 weeks, but varying widely, depending on individual response and ability to handle the therapy without side effects. One study claimed that 63% of MCS patients treated in this manner showed a reduction in levels of toxic chemicals after completing the course of treatment, and 86% of patients showed either clearing or marked reduction in symptom scores [244]. Another study showed normalization of cortical areas of the SPECT scan after detoxification [178].

d) Chelation Therapy

There may be a role for chelation therapy in some patients. This is the standard approach to heavy metal poisoning, aiming to mobilize and excrete the toxic metals; it is used particularly for accidental poisonings with lead, mercury, cadmium and aluminium, and in patients with iron overload from repeated transfusions. Chelating substances differ in their capacity to bind individual heavy metals; most are given by infusion but some are effective by mouth. They have been shown to increase excretion of excess iron, mercury, lead and aluminium [245–248] and benefit patients with overload. In addition to ethylene diamine

tetra-acetic acid (EDTA); desferoxamine, di-mercapto-succinic acid (DMSA), sodium 2,3mercapto-propane sulphonyl (DMPS) and deferiprone are used and others are under development.

The role of chelation in other circumstances is more controversial but it has been suggested that chelation to lower aluminium burdens might slow the development of Alzheimer's disease and some other neurodegenerative disorders [249]. Renal disease associated with moderate lead burdens has responded to chelation with improved creatinine clearance and disappearance of immune deposits [249,250]. Excretion of mercury was increased in patients with chronic symptoms attributed to amalgam fillings [246,247] but no clear symptom benefit was shown. Studies about chronic vascular disease have yielded conflicting data with some groups claiming marked improvements [251,252].

A number of toxic metals (lead, cadmium, aluminium and mercury especially) can be found in tissues from virtually everyone from birth onwards, the concentrations usually increasing with age [253]. It is theoretically possible that chronic accumulation of heavy metals lowers the threshold for the provocation of MCS and allergic diseases, in which case reduction of the load might be beneficial. Reducing the load of heavy metals in the mother before conception may well be of value in protecting the brain development of the foetus. Another possibility is that similar techniques may be effective in reducing the burden of synthetic organic chemicals in exposed individuals, and contribute to the management of MCS patients. We know of no firm evidence that this is so.

e) Low-dose Desensitization

Doctors who use these methods find that some patients with MCS are helped by the low dosage immunotherapy techniques, neutralization (also called relief dilution therapy) and enzyme potentiated desensitization (EPD) [1,9,254,255]. Double-blind studies with biological airborne allergens in rhinitis and asthma have demonstrated the effectiveness of each of the methods [256], including recent studies in the UK [257,258], and both neutralization [9,259] and EPD [255,260] therapy using food extracts have shown significant benefit in double-blind studies in patients with Type B food allergies. However, there have been no good studies of either technique using chemical incitants, although published clinical reports [6,165,175,176], the experiences of clinicians using these therapies, and reports about individual patients all suggest that the use of neutralization with chemical incitants has increased the patients' tolerance of exposure. A version of EPD utilizing very low concentrations of chemical incitants has recently been introduced and some clinicians have found it helpful in MCS.

The fact that these techniques are also of benefit in IgE-mediated pollinosis and house dust mite allergy, suggests that at least some part of the MCS syndrome may be due to an allergic response.

f) Psychological Therapies

In the past, chemically affected patients have been regarded as suffering from psychologically caused symptoms and subjected to a variety of psychological therapies. However, no convincing or definitive evidence to establish that psychological factors are causal has been published [179,180], although psychological symptoms certainly occur, some provoked by chemical exposures [164,177] and others induced by the stress of suffering a chronic illness for which no adequate explanation or treatment has been forthcoming [181,261]. The degree of improvement reported with psychological therapies [168–171] has been consistent with good management of secondary psychological symptoms; when these are present psychological therapies may be a helpful adjunct to other constructive methods. However, if the reality of a connection between symptoms and

environmental triggers experienced consistently by the patient is denied, such treatment may be actually harmful [261].

11. THE ROLE OF THE ENVIRONMENTALLY CONTROLLED UNIT IN MULTIPLE CHEMICAL SENSITIVITY

Buildings are polluted to varying degrees by biological and chemical substances coming from the structure of the building itself, from its contents, from activities within it and from the surrounding environment. Individuals may be sensitive to any of these, and if they are present during the testing process they may act as confounding factors, obscuring or distorting the results.

Confounding effects of aeroallergens and chemicals were first noted by Dr Theron Randolph in the USA in the early 1960s when he was investigating patients with chronic illnesses in a hospital side ward to find out whether food intolerance contributed to their illnesses [262]. Over the next 20 years he progressively eliminated these sources of pollution from his units, finding a steady increase in the proportion of patients whose problems could be relieved. Dr WJ Rea followed him and instituted an environmentally controlled unit in Dallas, Texas. These units were established by modifying existing buildings, using ceramic tiling, stainless steel and filtration of the air and water. The Dallas unit suffered from the disadvantage of being situated in a highly polluted area so that air intake, even through filters, had to be limited to night time when pollution was lowest [239]. Strict regimes were established in both units to exclude other sources of pollution and they succeeded in showing that the symptoms of substantial numbers of patients could be relieved if chemical incitants could be identified in addition to inhalant and food factors, and protection given for all of them [263–265]; similar findings have been reported in the UK [175,176,266].

The world's first purpose built environmentally controlled unit, the Airedale Allergy Centre (AAC), was opened close to the Yorkshire Dales in 1985 by Dr DJ Maberly, a consultant physician, as a private venture when his Health Authority had not felt able to cooperate in such a development. It was built of materials which do not outgas VOCs, equipped with sealed windows, double doors, a high rate of ventilation (producing slight positive pressure) with effective particle filters and activated carbon filters (to remove chemical pollutants), and a high standard of water filtration. Fittings and furnishings were of metal, hardwood and natural fabrics. The staff adhered to strict standards so that nothing perfumed or giving off VOCs was allowed into the building. In the 14 years after that, many patients who had consulted conventional physicians and surgeons of many specialties without lasting benefit were admitted, and discovered that their chronic illness was of environmental origin and learnt how to keep well [175,176, 266].

The regime at the AAC followed that developed in the USA, starting with a five-day fast. When a patient fasts in a clean environment, environmentallycaused symptoms usually resolve [3,9,176,239,267], although those provoked by chemicals may be slower to resolve than those due to foods [175]. Following the fast, oral challenge tests of single foods were given three times a day [268], interrupting the food schedule towards the end of the stay to allow testing of each relevant chemical and chemical mixture [269]. The regime depends on the use of neutralization (*see section on Low-dose Desensitization*), both to allow the testing of three foods most days (by curtailing the duration of the symptoms provoked), and to give protection against inhalant, food and chemical sensitivities on discharge, so that patients can maintain most of their improvement at home. Of the patients admitted to the AAC, over half have been sensitive to chemicals, some to only a few, but others to all those employed for testing.

Seventy per cent of patients admitted had remained much better when followed up at least 6 months after the 3-week admission [176]. On admission 41% were 'frequently incapacitated' falling to 9% on follow-up; and 3% had stated that their symptoms disrupted

their life 'scarcely at all' on admission, rising to 56% on follow-up. They had fewer symptoms—the median number of symptoms that were both severe and frequent fell from five before admission to one on follow-up [176]. This group of patients was selected for the severity of their illness, representing about a fifth of all patients referred for an allergy opinion, in addition to some in whom outpatient environmental investigation had been unsuccessful (mainly because of environmental exposures at home) and some tertiary referrals from other environmental physicians. The remaining four-fifths of referred patients were treated as outpatients with comparable results.

Unfortunately the unit was forced to close in May 1999 because the arrangements for NHS funding of extra-contractual referrals were changed and the incoming funding bodies were not confident about the funds at their disposal and refused (or delayed) approvals of funding for patients who had been referred, making it impossible to maintain the labour-intensive unit. Prior to that most patients had received NHS funding.

12. RESEARCH PRIORITIES

When Ashford and Miller, two highly respected independent scientists, surveyed the literature on MCS in 1988 on behalf of the State of New Jersey, they found enough evidence to convince them that there was a problem, but little research [270]; their report was subsequently published in book form [271], as one of the best summaries of the complex issues of MCS. Most of the work they reviewed had come from interested doctors who found *in practice* that a range of complaints could be relieved if they were treated as if they were reactions to environmental factors or foods. The research was therefore widely regarded as biased.

When the same authors were preparing for the second edition of their book *Chemical Exposures: Low Levels and High Stakes* [7] 10 years later the situation had changed considerably. Much of the research done in the interval had come from university scientists. The authors reviewed the research, criticizing much of it on the grounds that it did not ask the right questions (indicating lack of understanding of the problem), or showed inappropriate study planning. With this we concur. For instance, some biological and immunological studies compared individuals with MCS with 'normals', without any reference to whether their subjects had recently been exposed to chemicals or not.

The UK Health and Safety Executive commissioned another review of the data by independent scientists which has recently been published [8]: they also came to the view that 'the collated evidence suggests that MCS does exist', although there is still much need for research in this area, particularly in relation to mechanisms and prevalence.

As late as January 1999 academic immunologists in the USA were dismissive of the reality of MCS [272] in spite of reviews of research on the topic at a number of symposia and workshops [17–21] and in independent reports [7,8]. If MCS is an allergic phenomenon (the hypothesis currently showing the best fit), findings in patients who were completely avoiding the chemicals to which they were sensitized would not necessarily differ from findings in controls; in hay fever patients reactive only to grass pollen, levels of IgE and basophils in the blood fall during the winter [273]. At the US Symposium on Experimental Approaches to MCS [21], all the relevant working groups clearly recognized that baseline research data could only be acceptable in patients with MCS if the subject had been admitted to an environmentally controlled unit for several days before testing. Under any other circumstances there is a substantial risk of the baseline data being flawed, which would reduce or eliminate any difference on exposure. Comparisons need to be made between persons with and without MCS in unexposed and exposed circumstances. Results of the investigation of a number of parameters in a single patient, apparently sensitive only to a hairspray, before and after repeated blind exposure to the hairspray or a specially produced placebo are given in Appendix 2.

Research is especially needed in the following areas:

- Tests for diagnosis. In spite of many official findings and statements concerning the 'legitimacy' of the diagnosis of MCS, in some circles the diagnosis is still regarded as unproven. This has caused patients to have difficulties with jobs, friends, housing and benefits. A clearly acceptable diagnostic test would remove the stigma and provide a firm base for scientific studies of the condition.
- Studies of the chemical burden of different groups in the population.
- Studies of the prevalence of MCS. None has been done in the UK and any studies undertaken must be carefully planned; the methods used in population studies, commissioned by Government, of the prevalence of food additive intolerance and food intolerance were seriously flawed [274].
- Studies to elucidate the mechanisms involved. There are indications that the responses of different species to chemicals may differ (for instance penicillin is lethal to guinea pigs) so studies in experimental animals have limited relevance. As far as possible, studies should be in humans; for these to be valid, sufferers must be admitted to a clean environment (an environmentally controlled unit) for several days before testing.
- Studies to evaluate whether low exposures to synthetic pesticides and related compounds carry increased risk of the development of TILT.
- Studies into the possible interactions between the effect *in vivo* of the various chemical compounds that are widely used and/or widely dispersed.
- Evaluation of management methods. There are no good studies of the effectiveness of management except in the context of the audit of environmental management of consecutive patients [176,275] and in illnesses such as asthma [175,227], and cardiac and vascular conditions [263–265], apart from evidence of the reduction of the body load of chemicals using detoxification methods in acutely exposed populations [178,241–244]. There is a particularly urgent need for proper evaluation of low-dose desensitization methods, of nutritional support, and of detoxification; these are viewed with suspicion by doctors in general.
- A prospective study to see whether the rate of birth defects, low birthweight babies or the prevalence of allergies in children could be reduced by an intensive campaign to reduce the use of cigarettes, pesticides, perfumed products, aerosols and air fresheners, to control local sources of pollution, and to increase indoor ventilation. Comparisons could be made between co-operating and control towns and with data from previous years.
- A study added to that above, using a cross randomized format, to discover whether increasing the intake of a balanced range of nutrients would offer additional protection, since there are interactions between nutrition and foetal susceptibility to toxicants. This could be done by providing potential parents in some co-operating and control towns with an adequate nutritional supplement (in addition to folic acid) such as that used in Hungary [276,277], or in the Foresight study [278].

13. CONCLUSIONS

There is increasing disquiet about the safety of the chemical exposures experienced daily by people in industrialized societies [7,8,201,279,280], together with a realization that, at least in the short term, the problem does not lend itself either to reliable scientific evaluation or to easy solutions. Although mention is increasingly being made of 'the precautionary principle', little is being done.

From the standpoint of clinicians regularly faced with patients who are suffering from MCS, there are three priorities—to try to halt what appears to be a steady rise in the prevalence of MCS, to improve the recognition and management of MCS, and to increase awareness of the plight of these patients so that their associates will modify their behaviour and avoid turning them into social outcasts. Current data (*see section on Volatile Organic Chemical Concentrations and Late Symptoms*) suggest that

initiation of MCS would be less likely if exposures to synthetic and pollutant chemicals (particularly pesticides) were reduced, and ambient VOC levels kept below about 5 ppb (varying perhaps with different mixtures of VOCs). Widespread adherence to these maxima should cut down sensitization and therefore the need for the stricter limits on VOC concentration required for the protection of those sensitized. These precautions should also substantially reduce the risks of chronic toxicity.

We view with particular concern:

- the use of synthetic pesticides on foods, in houses, on gardens or playing fields, on pets and on people and especially their use on children to control lice infestation for which an effective non-toxic method is available [281]
- the consumption of foods, drinks and sweets containing unnecessary dyes and other synthetic additives, especially by children
- the unacceptably high prevalence of certain micronutrient deficiencies in the population; these increase the risks of ill-effects from marginally toxic exposures
- the fact that most homes are made energy-efficient by reducing ventilation, the occupants being unaware that indoor pollution is generally several times higher than that outdoors
- the existence of localized areas of severe pollution
- the widespread ignorance about the combustion products of gas appliances in normal use, the volatility of fragrances, and the VOCs given off by synthetic materials.

14. RECOMMENDATIONS

In our view action is needed urgently to increase the awareness of the general public about the risks and how they can reduce them, and to make sufficient funds available to attract independent researchers to address the topic. Government needs to show its commitment to preventing illness by tackling the problem of chemical exposures, if necessary including legislation.

a) General Awareness

It is of vital importance to raise the awareness of the general public on this issue. Members of the public are now leading the way on a range of safety issues, and more would do so if they were fully aware of the position. The quickest way to reduce the unnecessary dyes and other additives in food and drink and the odour pollution caused by cleaning products would be for the general public to refuse to buy them. Demand from the public has already forced the supermarkets to provide more organic food and foods with fewer additives. If enough shoppers shunned strong-smelling toiletries (especially aftershave, deodorants and cheap perfumes) and volatilizing fabrics, building materials and household products (air fresheners, aerosols, cleaning products with a strong odour, washing powders and fabric conditioners which can be smelled on the clothes), the range of products available would change quite quickly. Some retailers are already providing less noxious fabrics and building materials, and others would join them if the commercial pressures were strong enough. The alternative products are not always more expensive; 'real' food is cheaper and more wholesome than made-up dishes and not much more time-consuming; opening the window lets out the fusty smells and admits fresh air.

b) Medical Education

The contribution of environmental exposures to the provocation of chronic illness is not adequately covered in the undergraduate medical curriculum or during postgraduate training in the UK. There is some teaching about lifestyle risks (smoking, drug dependence, diet), mainly in relation to vascular diseases, chronic lung diseases and cancer, and a small

amount of tuition about atopy and the diseases to which it contributes (rhinitis, asthma, eczema, urticaria, acute gastrointestinal conditions and anaphylaxis). However, the role of other types of adverse reaction to environmental factors and foods in the aetiology of chronic illness is almost entirely ignored, as is the protective role of essential nutrients. It is important that future doctors are taught about these aetiological factors, so that they can recognize them and help patients to prevent symptoms, rather than continuing to suppress them with medication.

At the time of the official US report [282] on the role of primary care physicians in occupational and environmental medicine, there were virtually no academic experts in environmental medicine in medical schools in the USA, and few in occupational medicine. The report pointed out that adequate teaching of these subjects depended on the appointment of such staff and that the supply was unlikely to grow substantially until adequate funds were available for research in this area. If the medical schools in the UK wished to start teaching clinical environmental medicine, there are few people who would qualify for appointment to such posts at the present time. This partly results from the high proportion of medical research funding that comes from pharmacological companies who naturally see the extension of clinical environmental medicine as a threat. If worthwhile progress is to be made, funds for clinical environmental medical research must be made available; such funding would probably need to be ring-fenced for some years.

c) Research

There is an urgent need for research to improve the sensitivity of monitoring of environmental and food hazards, to discover the prevalence of chemically induced problems in the UK, and to establish effective means of diagnosis and treatment. Research should aim to tease out precisely what role chemical pollutants are playing in the increase of chronic illness (especially in patients with 'medically unexplained' conditions and/or multiple symptoms) and the extent to which synthetic and pollutant chemicals contribute to allergies, infertility, miscarriage and illness in infants and children, paying particular attention to the build-up of body burdens of pesticides and persistent organic pollutants in both sexes before they reproduce.

Research must be independent and adequately funded. A high-level conference of academics and clinicians is needed, restricted to those with no interests in or funding from chemical companies, but with the power to commission research into these topics and the ability to assess the data.

d) Government Action

In the past UK regulatory policy has been permissive: a development is legal unless it has been banned. By contrast many continental countries have based their law on the Code Napoléon. This legitimizes developments only after specific permission has been enacted. Our policies have served us well in the past, in for example the field of engineering, where entrepreneurs have been free to experiment and reap the rewards of their enterprise.

However, in respect of the development of chemical compounds, we argue that the time has come for a change to a more regulated legal framework where products reach an unrestricted open market only after adequate evidence has been obtained. There may be a long delay before the consequences of mistakes with chemicals are fully known; by then the genie is out of the bottle and difficult (or impossible) to put back. We already have problems with chemicals and the probability is that we have not yet appreciated their full extent. Yet the defence is still offered that there is no established evidence of harm. However, ***lack of evidence of effect is not evidence of lack of effect***. We consider that the indications are strong enough to call for a radical change in licensing policy, and in advertising policy.

We recognize the difficulties this would entail, made much greater by the economic importance and power of the chemical companies both in the UK and worldwide. We also recognize that decisions are dependent on the degree of risk that is recognized. However, individuals currently cannot choose to avoid chemical exposures, and even reducing them is both expensive and socially isolating. Risk benefit estimates are impossible in this area at the present time but if our reading of the situation is correct (*see section on The Prevalence of Multiple Chemical Sensitivity*), in addition to known acute risks, the overall chronic risk element could add as many as 8 million adults in the UK suffering from MCS. If, as a conservative estimate, a quarter of the population suffers from TILT, and if chemical exposures are a strong predisposing factor, no estimate of the benefits of, or to, the chemical industry would justify a policy of merely 'hoping for the best'. It is essential that there is properly informed scientific debate and investigation, and that all the information is made widely available.

The ideal application of the precautionary principle—that the use of chemicals should be permitted only after their use has been proved to be safe—is not feasible; safety cannot be *proved* either for chemicals already in use, or for new introductions, and the cost and time involved in even bringing the testing of all chemicals in general use up to the present standards would be prohibitive. The chemical industry is pressing for the risks from each chemical to be assessed, not only on the hazards it presents, but also on the numbers of people exposed to [23]. We support this and urge that, under the precautionary principle, consideration is given to restricting exposure to chemical substances to which the general population is most exposed (or for which there is evidence of accumulation) if there is *any* evidence of possible long-term ill effects.

We would press for Government to:

- review the permissions needed before chemicals can be synthesized for use in household products (bearing in mind that they are absorbed by multiple routes), and include assessments of interaction and of immunological adjuvant activity and hormone mimicry
- initiate work to increase the sensitivity of the methods used for monitoring the levels of pesticide residues or persistent organic pollutants (POPs) in food and drink, and increase the frequency of monitoring, publishing the results both in absolute terms and in terms of yearly intake on average consumption
- work towards a position where any food or drink in which pesticide residue or POPs can be detected will be considered unfit for consumption
- encourage manufacturers to use cleaning compounds whose odour does not need to be masked by strong fragrances and ensure that products free of artificial fragrances are readily available
- discourage the use of chemically synthesized fragrances, colourings and flavourings in foods, drinks and medicines, and the use of colour and fragrance in advertisements for foods and drinks which contain synthetic products, especially those aimed at children
- increase the monitoring of the air, soil and water in and near chemical plants, waste plants, power stations etc, and support, and investigate thoroughly, all complaints about chemical contamination made by employees and people living near such plants
- give much more support to the development of organic farming
- ensure that information on chemical exposures, the effects of such exposures and the phenomenon of MCS is freely available to the public.

None of this would be easy; the issue urgently needs a proper high-level informed scientific conference with power to initiate some action. To be acceptable, changes may have to be phased, but to fail to act is likely to result in even higher costs as well as serious effects on those as yet unborn. We have reason to believe that even minor changes would slow the increase in chronic ill health, and that, if the pace of change accelerated, a substantial reduction of the personal and social burden of chronic illness would follow, with a reduction of the economic burden on the NHS.

APPENDIX 1. ILLUSTRATIVE CASE REPORTS

In patients suffering from severe MCS, multiple symptoms are provoked by a range of different factors, natural and chemical, and the events which contributed to initiation of the sensitized state are often uncertain; case histories have been published, for instance the proceedings of two symposia include a full case history contributed by a clinician [6] and descriptions by the patients themselves [18]. The brief case histories given here are, to some extent, atypical in that they have been chosen because they demonstrate a likely initiating exposure, a limited sensitivity to chemicals provoking physical symptoms, or an aspect of management. Other case histories in the literature report the development of MCS from home environments [230], after accidental contamination from crop spraying [97] or after anaesthetics [283], immediate-type reactivity to dyes [160,284], amalgam allergy [285], and chemical sensitivity to metabolites [151,152].

Case 1: Sensitivity to Gas

This was a middle-aged woman with a five-year history of severe sero-negative arthritis who had consulted eminent rheumatologists in London and Switzerland. She had continued to have severe pain in spite of taking oral steroids and having multiple steroid injections into various affected joints.

When she undertook an elimination diet, there was a transient worsening of her symptoms but by the sixth day there was a marked improvement. Joint symptoms subsequently recurred on challenge with orange, lemon, grapefruit, wine vinegar and raspberries, particularly severe with orange which she had had regularly every morning. Avoiding these foods she described herself as 70% better.

Shortly afterwards she went to stay with her mother in Switzerland, continuing on her diet. Within a couple of days she became symptom-free, and at first attributed this to a late effect of the dietary regime. However, many of the joint pains recurred within 48 h of returning home. The flat in Zurich was all-electric, whereas at home she had a gas cooker and gas-fired central heating. As a test she was asked to turn off all her gas appliances at the mains and to make sure that the house was well ventilated. Within a few days she was as well as she had been in Switzerland; 2 days after turning them on again the pain recurred. She then replaced her gas cooker with an electric one and arranged for the gas central-heating boiler to be re-sited in an outhouse. This was more than five years ago and she has had no recurrence of symptoms since.

Case 2: Sensitivity to Water Contaminants

A 29-year old male business executive with a strong family history of allergies started to suffer from recurrent sore throats and headaches in his teens, and from insomnia, fatigue, malaise and irritable bowel syndrome in his twenties.

He left home for university at the age of 17 and found that his sore throats and headaches completely cleared, but returned on visiting home. The only apparent difference at college appeared to be the tap water. When he started to use bottled water on home visits he was able to be symptom-free at home as well as away, and has continued to avoid tap water. If he ingests it by chance he develops a sore throat, headaches and swollen neck glands within 24 h which clear on avoidance within 3 days. Shortly after leaving the university he developed other symptoms, and was found to have developed other intolerances, including intolerance to some foods.

Sensitivity to tap water is not uncommon but it is very unusual for it to be the first presenting sensitivity.

Case 3: Particle Board Flooring

A woman developed periorbital swelling soon after moving to a newly built house with

particle board flooring, but resisted any suggestion of a connection. She had a history of other symptoms for several years, including irritable bowel syndrome and migraine; these were relieved by an elimination diet and the avoidance of a few incitant foods, but periorbital oedema and general malaise remained. She attended for chemical testing which was negative, even for formaldehyde, the most common incitant associated with particle boards. No funds were available for admission to the environmental unit so she went back for testing immediately after a 3-week holiday in a tent in the Yorkshire Dales, without going back into her house; the formaldehyde challenge was strongly positive. She did not want to move again and made major house changes, reflooring with wooden boards, starting with the bedroom. After this the oedema settled, but it was only when about half the floors in the house had been done that she felt generally better and started to recognize that VOCs in some shops provoked symptoms.

Case 4: Sick Building Syndrome

This lady was first seen in 1990, at the age of 44. She was employed as an administrator in the head office of a major electronics company; within the past year they had moved to a new building.

Within weeks of the transfer she had started to feel tired and light-headed and complained of dry hair, scalp and skin. She had one episode when she felt particularly bad and was going out of the building for fresh air when she collapsed in the reception area. She was stated to have lost consciousness, but by the time she was examined in the accident and emergency department of the local hospital some 30 min later she was conscious and no abnormal physical signs were found.

A multi-disciplinary investigation was set up as a number of other workers had become ill (*see section on Sick Building Syndrome*). When examined, this patient was found to be an allergic subject who had hay fever; her hyperventilation score was borderline. A skin prick test to grass pollen was positive in the immediate phase only, but prick tests to other classical aeroallergens, including house dust mite, were negative. An extract prepared from dust from the building gave a borderline response at 10 min, but then increased in size and persisted overnight with severe itch requiring antihistamines. The patient went on to develop a mild fatigue syndrome; no abnormalities were found by a neurologist.

A physiotherapy programme of breathing retraining was set up for all the workers who had collapsed, including this patient. Steps were taken to reduce chemical pollution in the building by improving the function of the HVAC, to increase ventilation and to reduce sources of VOCs. Her work station was opposite that of a heavy smoker; when a smoking ban was introduced, there was a substantial improvement in her condition. Subsequently she went on improving and was able to continue to work in the building without complaint.

Case 5: Multiple Chemical Sensitivity Initiated by Organo-phosphate Pesticides

A 29-year-old sheep farmer had been completely fit and well until 5 years previously when he took on a scanning business. The business entails using ultrasound scanning to diagnose pregnancy and predict numbers of offspring, so sheep can be managed appropriately, and involved scanning 60 000 sheep during the winter months in the UK and 100 000 during the summer in New Zealand. The job had been vacated by a young man who died from primary hepatoma 5 years after starting this work. OP residues are retained in wool for many months after dipping and so there was very significant exposure to OPs. The farmer remained reasonably well for the first 12 months then noticed increasing thirst, developed an irritable bowel syndrome and fatigue. Investigations including barium meal, endoscopy and ultrasound liver scan demonstrated a small hiatus hernia. He then went on a rugby trip, got drunk, and all his symptoms got very much worse. When he restarted work after this

break he found he was reacting with acidity and stomach churning to the paint spray used for marking sheep after they had been scanned. He developed numbness in his toes and thumbs and itching skin. He also found he was reacting to the navel antiseptic sprays that he used during lambing, and the foot rot bath. This contains a solution of formaldehyde through which the sheep walk (or rather run as it is obviously painful to them!) and which has a very offensive smell.

At this point he consulted an environmental physician who diagnosed MCS on the basis of the history, advised him to avoid OPs and any other chemicals to which he was obviously reacting. A gut fermentation test was positive and a low sugar diet was prescribed along with a range of micronutrient supplements. He improved.

By dint of using the paint sprays carefully and not scanning recently dipped sheep, he was able to continue his business, despite constantly feeling unwell. He had realized by now that OPs were a problem for him, so when dipping time came he decided to use the "farmer friendly" sheep dip based on cypermethrin. He dipped 1300 ewes on his own. There were no indications on the tin of concentrate about using protective clothing and so he dipped in jeans, trainers and tee shirt. Two days later he developed classical sheep dip flu with fever, rigors, shivering, light headedness, pins and needles followed by numbness in his hands (reported to the Poisons Unit, Cardiff). This reaction took 10 days to clear and he continued to be unwell for a further 4 weeks before making a good recovery. However he then found he was reacting to wheat, yeast, cocoa and pineapple and had to avoid these foods to remain well.

Subsequently he found he was reacting violently to the smell of OP dip. This became apparent during a trip to market. He was unable to continue his scanning business, but has remained well since, as long as he scrupulously avoids chemical exposure.

Case 6: Silicone Face Lift

This patient was fit and well up to 1991 when, at 27 years of age, she had silicone injections into her face in order to iron out horizontal creases in her forehead. She received 20–25 injections a session during 5 separate 10 min sessions. Each session was followed by local redness and swelling, treated by steroid creams. Later, steroid injections were given into the face to control the local reaction to silicone. The overall cosmetic result was most unsatisfactory, partly because she developed skin atrophy after the steroid injections.

Within a few weeks of these injections she developed facial pain and had to be referred to the pain clinic. She also developed increasing fatigue typical of chronic fatigue syndrome and episodic blurred vision. In April 1993 she developed sero-negative arthritis requiring salazopyrine.

By September 1997 she had ongoing neurological symptoms with loss of balance, blurred vision, and abnormal visual evoked potentials. MRI scan showed demyelination typical of multiple sclerosis. Antipolymer antibody testing showed high titres.

Case 7: Silicone Breast Implant

In 1983, at 36 years of age, this patient had a mastectomy for cancer followed by local radiotherapy. She did very well and in 1988 decided to have reconstructive surgery with a silicone implant inserted into the remains of her left breast. Following the operation she developed local tightness, pain and hardening of the breast treated by closed capsulotomy whereby the breast is crushed between the surgeon's fists to rupture the scar capsule. Soon afterwards a lump in the left arm was noticed, biopsy of which revealed silicone. The ruptured implant was removed in 1989, but multiple nodules remained in the left axilla; clinically these feel like a bunch of grapes. Needle aspirations demonstrated free silicone and silicone granulomas, but because of their close proximity to the brachial plexus, surgery was not feasible.

She now has a severe brachial neuritis with chronic pain in her left axilla and arm, and weakness and clumsiness of that limb. She also has a burning sensation in the left side of her neck and over the left side of her chest so that respiration is painful.

She used to be very fit. Since her implant she has developed increasing fatigue, chest pains and palpitations, recurrent headache and rashes. She became intolerant of foods and chemicals. By dint of avoiding certain foods (mammal meats, potato and wheat) and strictly avoiding exposure to chemicals she can remain reasonably well.

APPENDIX 2. INVESTIGATION REPORT (J. McLaren Howard, February 1999)

Repeated Investigation of a Patient Apparently Sensitive Only to Hair Spray

This was a 41-year-old female teacher who consulted with reactions to a specific hair spray, which she continued to use in spite of them. Reactions consisted of a scaly, itchy, macular skin rash, headaches and relatively minor fatigue which lasted for 2–3 days after each use. After the investigations were completed she decided to stop using the hairspray.

- The patient volunteered to be studied before and after use of the spray, which she applied herself, double-blind. The studies were performed over a total of 3 sessions.
- During each session she was studied a) before each challenge, b) after challenge with the standard hairspray and c) after placebo challenge using a product visually indistinguishable from the standard hairspray, made by manufacturer without two most likely triggers, shellac and a synthetic compound. Challenges were given double-blind and in random order.
- The first pre-challenge value for each session and the post-challenge readings are given: if the second pre-challenge value was different, the difference has been subtracted from corresponding post-challenge value.

Results

a. Pulse

Session	Pre	Placebo	Challenge
1	68	70	76
2	66	70	84
3	72	72	80

b. Respiration

Session	Pre	Placebo	Challenge
1	17	19	19
2	16	18	23
3	17	17	22

c. Transcutaneous PO2, palm of hand

Session	Pre	Placebo	Challenge
1	68	68	54
2	64	67	52
3	67	69	58

Presumptive evidence of the induction of autonomic dysfunction, with vasospasm.

d. Doppler Studies (Using Computerized Doppler Ultrasound)

A reduction in peripheral pulsatility occurred within one minute of challenge but not with placebo. Measured at the pedal artery, the mean reductions (measurements made on three separate occasions) were from 15.8 to 12.6 using the peak-to-peak method and from 16.4 to 11.3 by the Fourier transform method.

There were also qualitative changes in the degree of Radial/Ulnar shunting, but these were not quantified.

e. Systolic Pressure

Ankle systolic pressure slope normalized by dividing it by the brachial systolic pressure.

Session	Pre	Placebo	Challenge
1	4.2	4.2	3.9
2	4.2	4.2	4.0
3	4.2	4.1	3.8

The challenge values taken alone would be interpreted as atherosclerosis.

f. Bioelectrical Impedence

Measured across the chest cavity (anterior to L axilla and lateral aspect R lower chest)

Session	Pre	Placebo	Challenge
1	182	189	194
2	177	180	205
3	190	190	212

g. Gamma-GT

Changes not expected because the exposure was not considered to be toxic.

Session	Pre	Placebo	Challenge
1	16	21	23
2	18	19	22
3	16	19	21

Surprisingly, increases in gamma-GT isoenzyme 3 were detected in the post-challenge serum samples but not in the pre-challenge or placebo challenge sera. Raised levels of iso-enzyme 3 are usually associated with alcohol intake, hyperthyroidism or, when the bilirubin is also increased, with hepatitis or cirrhosis.

h. Pesticide Profile in Serum

The pre-challenge profile demonstrated background exposure levels of Lindane, DDT and PCBs. After challenge and after placebo challenge a small peak representing 0.5 μgl^{-1} of Toxaphene was present in the chromatogram.

After challenge, but not after placebo, there was a fourfold increase in DDT and Lindane levels but no change in PCBs.

Toxaphene, DDT and Lindane were not present in the spray or placebo. They may have been mobilized from the patient's fat cells. The trace of Toxaphene may have been a fat cell response to the ethanol present in both the placebo and the fully formulated spray.

These changes were demonstrated in all three sessions and have subsequently been confirmed on three further occasions.

Conclusions

In this patient it was possible to quantify a number of changes in clinical and laboratory parameters following double-blind exposure to the specific hair spray but not to placebo. It should be noted that these findings were obtained in a mild case of chemical sensitivity; symptoms in this case were not severe enough for the patient to have decided against further use of the product. Such repeated exposures could not ethically be applied to patients where the reactions to challenge were severe, but this example does indicate the importance of careful co-ordination of clinical data, clinical test procedures and laboratory investigations, and the value of measurements taken before and after exposure.

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