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Low-level chemical sensitivity: current perspectives

Introduction

While sensitivity to low levels of chemical exposures is not a new problem, it has been approached with renewed interest. and controversy, in the last decade. first in North America and more recently in Europe. The Canadian government first examined the problem of chemical hyper-reactivity in 1985 in its Thomson Report (Thomson 1985) and has since sponsored several workshops to help define a research agenda in this area. In the United States, the issue has been discussed and examined by state governments (Ashford and Miller 1989; Bascom 1989), federal agencies. (ATSDR 1994), the National Academy of Sciences (NRC 1992), and a number of professional organizations through workshops. conferences. and position papers (AOEC 1992; ACP 1989; AMA 1992). Chemical hyper-reactivity continues to engender scientific debate and controversy around issues relating to etiology. diagnosis. and treatment. While an increasing number of patients voice their concern and dissatisfaction with the response of the medical community and government to their illnesses which they believe are caused by exposure to low levels of chemicals in their environments, the scientific debate rages on; and the medical community continues to engage in sometimes acrimonious discussions about the nature of the problem.

Since our overview of the problem in North America (Ashford and Miller 1991). we are increasingly persuaded that low-level chemical sensitivity, rather than a clearly-defined disease entity, might be more correctly described as a class of disorders–like infectious disease–the members of which may present with similar symptoms. but which have a myriad of precipitating agents and pathophysiological pathways. Chemical sensitivity may be viewed as the consequence of a variety of disease processes, while "toxin-induced loss of tolerance" may provide a phenomenological description of those processes (Miller 1995a).

In our continued thinking about the problem, we have noticed a certain illogic that attends the many observations made and approaches taken to unravelling this problem. We are especially struck by the errors in logic that confuse information relevant to cause, presentation and the evaluation of interventions related to the condition. The purposes of this paper are to draw upon our recent work and observations in order to (1) contribute to a clearer way of thinking about chemical sensitivity and (2) to underscore the value of narrowing the focus of future enquiry to observations of event-driven studies. rather than concentrate on characterizing collections of patients who present with chemical sensitivity which they identify as having originated with a myriad of different exposure events and at varying times in the past.

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Distinguishing different types of sensitivity

The different meanings of the term *sensitivity* are at least partially responsible for the confusion surrounding chemical sensitivity. Individuals differ in their responses to increasing doses of a toxic substance. The underlying causes of inter-individual variability include age, sex, and genetic makeup; lifestyle and behavioral factors, including nutritional and dietary factors. alcohol, tobacco and drug use; environmental factors; and preexisting disease (Ashford et al. 1990). In the *classical. toxicological* use of the word sensitivity. those individuals who require rela-
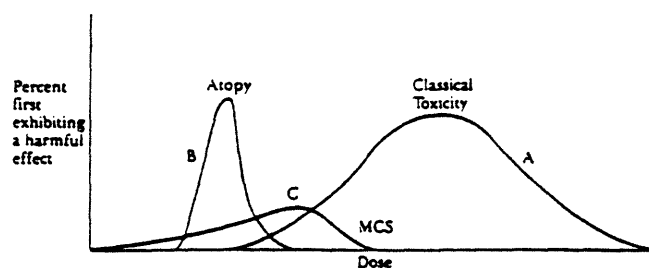
Fig. 1 Hypothetical distribution of different types of sensitivities as a function of dose. *Curve A* is a sensitivity distribution for classical toxicity, e.g., to lead or a solvent. Sensitive individuals are found in the left-hand tail of the distribution. *Curve B* is a sensitivity distribution of atopic or allergic individuals in the population who are sensitive to an allergen, e.g., ragweed or bee venom. *Curve C* is a sensitivity distribution for individuals with multiple chemical sensitivities who, because they are already sensitized, subsequently respond to particular incitants, e.g., formaldehyde or phenol

tively lower doses to induce a particular response are said to be more sensitive than those who would require relatively higher doses before experiencing the same response (Hattis et al. 1987). A hypothetical distribution of sensitivities, that is, the minimum doses necessary to cause individuals in a population to exhibit a harmful effect, is shown in curve A in Fig. 1. This distribution illustrates the traditional toxicological concept of sensitivity. Health effects associated with classical diseases are seen in a significant portion of the normal population as a result of exposure to a relatively narrow range of doses; the sensitive and resilient populations are found in the tails of the distribution. (Of course, not all toxic substances have small variances or significant tails.) For the classically sensitive person, avoidance of low-level exposures generally leads to improvement, or at least to the arrest of the development of the disease.

A second meaning of the word sensitivity appears in the context of classical IgE-mediated allergy (atopy). The atopic individual exhibits a reaction, whereas non-allergic persons do not, even at the highest doses normally found in the environment. A hypothetical sensitivity distribution for an atopic effect is shown in curve B of Fig. 1. Allergists include in the term allergy well-characterized immune responses that result from industrial exposure to certain chemicals, such as nickel or toluene diisocyanate (TDI). Most allergists refer to such responses as chemical sensitivity, but reserve this term for responses that have or appear to have a distinct immunological basis. They prefer to use a different term such as chemical intolerance for non-immunological responses to chemicals.

Patients suffering from what North Americans call multiple chemical sensitivity (MCS) (Cullen 1987) may exhibit a third and entirely different type of sensitivity. Their health problems often (but not always) appear to involve a two-step process. The first step originates with some acute or traumatic exposure, after which the triggering of symptoms and observed sensitivities occur at very low levels of chemical exposure (the second step). The in-

ducing chemical or substance may or may not be the same as the substances that thereafter provoke or "trigger" responses. (Sometimes the inducing substance is described as "sensitizing" the individual, and the affected person is termed a "sensitized" person.) Acute or traumatic exposures are not always necessary. Repeated or continuous lower-level exposures may also lead to sensitization. To date, there is no clear consensus on this staging process in the scientific community.

These "sensitized individuals" are not those on the tails of a normal distribution. They are thought to make up a distinct subset of the population. The fact that normal persons do not experience even at higher levels of exposure those symptoms that chemically sensitive patients describe at much lower levels of exposure probably helps explain the reluctance of some physicians to believe that the problems are physical in nature. To compound the problem of physician acceptance of this illness, multiple organ systems may be affected, and multiple substances may trigger the effects. Over time, sensitivities seem to spread, in terms of both the types of triggering substances and the systems affected (Randolph 1962).

Avoidance of the offending substances is reported to be effective but much more difficult to achieve for these patients than for classically sensitive patients because symptoms may occur at extremely low levels and the exposures are ubiquitous. Adaptation to chronic low-level exposure with consequent "masking" of symptoms is alleged to make it exceedingly difficult to discover these sensitivities and unravel the multifactorial triggering of symptoms (Ashford and Miller 1991). A hypothetical sensitivity distribution for a single symptom for the already chemically sensitive person in response to a single substance trigger is shown in curve C of Fig. 1. It should be emphasized that individuals who become chemically sensitive may have been exposed to an initial priming event that was toxic (e.g., neurotoxic) as classically defined. Conceivably, exposure to certain substances, such as formaldehyde, might elicit all three types of sensitivities.

Mechanisms to explain this third type of chemical sensitivity range from psychological to physiological – including neurological, immunological, and biochemical (or endocrinological) pathways (Ashford and Miller 1991). Odor conditioning, perhaps involving both psychological and physiological mechanisms, has also been suggested (Doty et al. 1988). For reviews of the North American literature on proposed mechanisms, see Ashford and Miller 1991; Sparks et al. 1994.

Subsequent to our review of the literature on low-level chemical sensitivity (Ashford and Miller 1991), one of us directed an investigation of low-level chemical sensitivity in nine European countries for the European Union (Ashford et al. 1995) and the other, in the largest study of chemically sensitive persons reported to date, compared the features of two groups with chemically distinct, but well-documented exposures preceding onset of self-reported chemical sensitivity.

In an attempt to define the population of interest in the European study, a multinational group of investigators

formulated the following taxonomy to guide its data collection activities and analysis. Chemical sensitivity encompasses three relatively distinct categories:

(1) The response of normal subjects to known exposures in a traditional dose-response fashion. This category includes classical allergy or other immunologically-mediated sensitivity.

(2) The response of normal subjects to known or unknown exposures, unexplained by classical or known mechanisms. This category includes:

(a) Sick building syndrome in which individuals respond to known or unknown exposures but whose symptoms resolve when they are not exposed to the building.

(b) Sensitivity, such as that induced by toluene diisocyanate (TDI), which begins as specific hypersensitivity to a single agent (or class of substances) but which may evolve into non-specific hyper-responsiveness described in category 3 below.

(3) The heightened, extraordinary, or unusual response of individuals to known or unknown exposures whose symptoms do not completely resolve upon removal from the exposures and/or whose "sensitivities" seem to spread to other agents. These individuals may experience: (a) a heightened response to agents at the same exposure levels as other individuals; (b) a response at lower levels than those that affect other individuals; and/or; (c) a response at an earlier time than that experienced by other individuals.

The European investigation focused primarily on categories 2b and 3 above. This focus essentially excluded traditional sick building syndrome, although hypersensitive sub-cohorts of individuals affected in tight buildings (that is, those individuals who might not have recovered, but who experienced subsequent sensitivities) were thought to constitute a potentially useful group who could provide important information on low-level chemical sensitivity (Chester and Levine 1994).

Separating cause and effect: distinguishing causes, effects and the results of interventions

In researching the presentation and characterization of low-level chemical sensitivity, it is useful to distinguish contrasting ways in which observations might be recorded. First, physician reports of individual patients can be examined. Since chemical sensitivity was first "discovered" by observant physicians, this might seem like a useful place to start, but there are difficulties with this approach. While physician reports contain much information about the patient's symptoms and complaints, they usually contain inadequate information about possible initiating exposures or events and outcomes of various interventions—both clinical and non-clinical. Moreover, information differentiating initiating events/exposures from subsequent sensitivities is often lacking or conceptually muddled. Since the precise nature of and mechanisms

for chemical sensitivity remain ill-defined, information on possible initiating factors and effective interventions is crucial to improving our understanding of this somewhat bewildering condition. Also, each of the more prevalent effects can be caused by a multitude of biological mechanisms and environmental exposures. Therefore, the symptoms do not indicate the nature of the causality, which may be multifactorial.

Most physicians do not usually obtain occupational or environmental histories on their patients, and the patients themselves may not be fully aware of possible precipitating events or exposures. Moreover, physicians approach patients with their own disciplinary orientations and biases, making it difficult to compare reports on individual patients from different physicians. (Of course, different patients with their own convictions about the cause of their condition may also influence their physician's diagnosis.) For example, pulmonary physicians will tend to focus on respiratory symptoms and airborne contaminants, perhaps overlooking or discounting the more subjective (and possibly equally bothersome) central nervous system (CNS) complaints. Indeed, chemically-sensitive patients often go from physician to physician, acquiring different diagnoses and labels – from organic brain syndrome to chronic fatigue syndrome to psychosomatic disease. Since there seems to be few proven effective medical interventions for these patients, the eventual outcome of the condition and possible success of various interventions (such as avoidance, food rotation, or simply just letting time pass) may not be known to the diagnosing physician or clinic.

Finally, isolated case reports suffer from being symptom/syndrome-focused in patients with health problems that might be induced by a wide variety of different initiating exposures or events. This has compounded the difficulty in understanding the origins of chemical sensitivity. We have earlier suggested that low-level chemical sensitivity might be more correctly described as a class of disorders, like infectious diseases, the members of which may present with similar symptoms, but whose different causes and pathways need to be particularized to successfully address them. The different forms of chemical sensitivity may be differentially precipitated by psychosocial events or stress, or by different physical or chemical exposures. The presenting symptoms – whether objective or subjective – are not necessarily indicative of etiology.

Causes, symptoms, and interventions can each be characterized as physiological (P) or psychological (Ψ). Both physiological and psychological stressors can precipitate either physiological or psychological symptoms, or both. Psychological interventions (such as biofeedback and social support) can alleviate some aspects of physical disease. Neither the nature of symptoms, nor the successes of interventions, are dispositive of the origins of a condition. Schematically, the three factors – causes, symptoms, and interventions – can be represented as separate "dimensions" of illness (Fig. 2). Physicians and researchers may operate in different "quadrants." For example, a physician may believe that the cause of a particular patient's chemi-
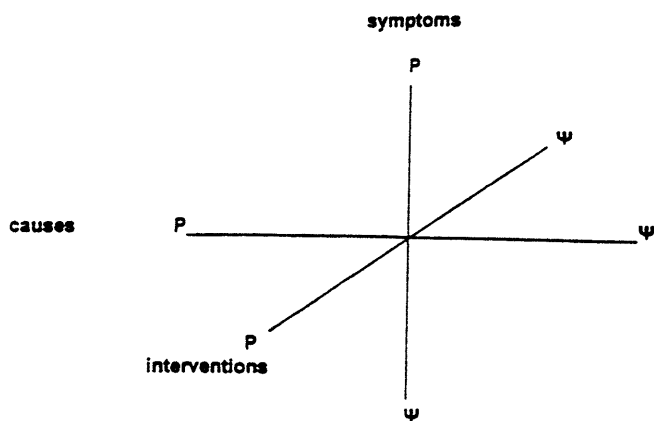
Fig. 2 Schematic representation of the three dimensions of illness

cal sensitivity is physiological. observe CNS (psychological) symptoms, and treat with biofeedback or other coping (i.e.. psychological/behavioral) interventions. In contrast. a researcher may assume stress as the "cause." observe asthma as a consequence. and investigate the use of new drugs to alleviate the symptoms.

What is disappointing in much of the literature is the continuing failure to distinguish causes and symptoms of the condition and unjustified conclusions drawn from successes or failures of possible interventions. Although lip service is given to making these distinctions. at the end of the day, the failure to find consistent objective markers of disease (Simon et al. 1993) or the finding of a history of childhood abuse in some patient groups (Staudenmayer et al. 1993) lead the authors to lean very heavily in the direction of psychogenic causes and the recommendation of psychological interventions, rather than physiologic causes and the avoidance of future exposures as a treatment modality. Even a recent review of some of the literature on low-level chemical sensitivity (Sparks et al. 1994), while acknowledging the multifactorial origins of this condition, ends up recommending psychological interventions as the only acceptable treatment modality. Inasmuch as great uncertainty continues to characterize this condition. these views are premature and perhaps even harmful to patients (Miller 1995b).

Empirical approaches to unraveling the mysteries of low-level chemical sensitivity

The need to distinguish information that might elucidate causes, presentation and the success of interventions having been discussed above. physicians' observations may be more helpful when: (1) the physician sees a large number of chemically-sensitive patients. takes a complete exposure history; and recognizes subgroups that give clues to different origins and successful interventions of each: (2) the physician happens to see a group of patients who have experienced the same or similar events or exposures, such as living in the same neighborhood or apartment building or using the same type of product, such as new

carpets; (3) the physician specializes in occupational or environmental medicine and sees patients with similar exposures. occupations, or environmental histories: or (4) the physicians are specialists – for example. pulmonary or ear. nose and throat physicians – who concentrate on specific organ systems and are more likely to recognize subsets of patients who present with problems uncharacteristic of the majority of patients with the same illness. For example, patients whose asthma is precipitated by perfumes. detergents, and clothing stores may constitute a chemically-sensitive subgroup of special interest. In order for these types of fortuitous observations to provide clarification of chemical sensitivity. the occurrence of some of the different presentations of chemical sensitivity would have to be reasonably large.

Perhaps more informative would be observations on the natural history of chemical sensitivity associated with particular incidents or exposure events rather than isolated case reports. Event-driven information includes both (1) disease or symptom outbreaks in particular communities. buildings, workplaces. or occupational groups and (2) events/scenarios reported as related to chemical exposures commonly found in certain occupations and those from particular building materials. consumer products. anesthetics, and ethical drugs. Studies of collected case reports or multiple case reports linked to specific incidents or exposure events might be particularly useful. Identification of events or exposures that could be followed over time may be more likely to be reported by public. environmental. or occupational health authorities. compensation or disability agencies, affected individuals. trade unions. and patient associations rather than by physicians. While retrospective investigations may be helpful. prospective studies (for example of greenhouse workers or occupants of newly-renovated office buildings) might yield useful perspectives. especially if the cohort is followed for a sufficiently long period of time.

We have previously cautioned about the necessity of accounting for adaptation or the masking of symptoms in observing the symptoms of patients with alleged low-level chemically sensitivity. the possible confounding of observations resulting from the use of therapeutic drugs, and the failure to investigate food intolerances in patients with possible low-level chemical sensitivities (Ashford and Miller 1991). Researchers and clinicians who ignore these concerns. and then find no consistent markers. symptoms, or success in chemical avoidance can not rightfully claim to have tested or investigated the many hypotheses suggested for this condition (Datta 1993).

Recent empirical work on event-driven observations

Miller and Mitzel (1995) recently completed a study in which they compared features of chemical sensitivity reported by two groups with chemically distinct but well-documented exposures preceding onset of self-reported chemical sensitivity – one group ($n = 37$) initially exposed to an organophosphate or carbamate cholinesterase-in-

hibiting pesticide (OP), and the other ($n = 75$) to remodeling of a building (RE). As opposed to chemical sensitivity patients with lifelong symptoms, these individuals reported becoming ill at a discrete point in time, and most were working full-time at the time of their exposure. It was felt that these two subgroups of patients should be better able to distinguish which symptoms were or were not related to the condition. In addition, OP and RE exposure groups were chosen because: (1) Many chemical sensitivity patients have reported one of these exposures as initiating their condition; (2) such exposures are likely to be readily identifiable; (3) pesticide spraying and building remodeling occur at discrete times, unlike protracted exposures of industrial workers to solvents; and (4) group differences, if present, should be due to differences in potency of the chemical compounds allegedly inducing the illness.

Individuals with self-reported chemical sensitivity were recruited via announcements in chemical sensitivity patient newsletters to ensure a sample of strictly self-identified chemical sensitivity respondents. Respondents were sent a mail-out/mail-back questionnaire which covered the exposure event, a brief medical history, and physical and cognitive symptoms occurring since their exposure. Two hundred-three questionnaires out of 379 mailed were returned (54%). To be included in the OP group, respondents had to report having developed chemical sensitivity as a consequence of a pesticide exposure, specify the month and year of exposure, and provide the name(s) of the organophosphate or carbamate pesticide(s) to which they had been exposed. To be included in the RE group, respondents had to report having developed chemical sensitivity as a consequence of exposure to remodeling of a building and specify the year and month in which the exposure occurred or began. Those who attributed their illness to both remodeling and organophosphate exposure or did not specify a cause were not included, since the purpose was to compare two groups of chemical sensitivity patients that identified distinctly different initiating events.

Questionnaires contained items pertaining to the circumstances of the exposure, checklists for 98 common inhalants and 46 common ingestants, severity ratings for 114 symptoms, questions concerning disability and quality of life issues, and the number and types of physicians consulted. Thirty-seven questionnaires qualified for inclusion in the OP group and 75 in the RE group. Completed surveys were received from 33 states and 3 foreign countries. Nearly four times as many females as males returned surveys. There were no statistically significant differences between OP and RE group means for age, education, years elapsed since exposure, or for gender ratios. The average time between exposure and survey completion was 7.7 years. Average age at onset of illness was 40 years.

OP exposures occurred in the workplace in 16 cases (43%), home in 20 cases (54%), and during outdoor recreation in 1 case. Proportionately more remodeling exposures occurred at work (51 cases, 68%) versus home (24

cases, 32%). Twenty-one OP respondents implicated a single pesticide, while 16 described mixed pesticide exposures. Organophosphates or carbamates most frequently named were chlorpyrifos (19), diazinon (9), malathion (6), and carbaryl (4). Although REs were not asked whether new carpeting was laid during the remodeling exposure, 59% mentioned new carpeting in their narrative descriptions. In response to an open-ended question concerning the exposure event, OPs reported neurological and cardiac symptoms as their earliest symptoms approximately twice as frequently as REs, and REs cited mucous membrane irritation and headache approximately twice as frequently as OPs.

Respondents were asked to identify their current, single most troublesome exposure. Among the 112 respondents, 28% reported insecticides, 18% new carpeting, and 11% perfume as their most problematic exposure. Twenty-three (21%) listed more than one exposure as being "worst." Four named formaldehyde and three diesel exhaust as "worst." Only one cited cigarette smoke as most problematic. Not unexpectedly, insecticides were cited by 68% of OP respondents, while building-related exposures (carpet, paint, varnish) were cited by 38% of RE respondents as their worst exposure. None of the OP respondents rated building-related exposures as "worst," but five of the RE respondents rated insecticides as causing the most difficulty for them at the time of the survey.

Symptom severity ratings were compared (1) on the basis of eight factored scales and (2) on the basis of symptoms heuristically selected for their discreetness and frequency in chemical sensitivity patients. An overall multivariate F-test of the eight factored scales was significantly different for the groups for exposure type ($p < 0.008$) but not for gender. None of the covariates (age, education, years since exposure) originally fit with the model was statistically significant, and all were dropped.

All symptom severity scale means were higher (more severe) for the OP than the RE group (Table 1). Based on univariate analyses of variance, symptom severities differed significantly between OPs and REs on five of the 8 factored scales: Neuromuscular, affective, airway, gastrointestinal, and cardiac symptoms were rated as more severe by OPs than REs. Muscle-related symptoms bordered on significance, with OPs higher than REs. Cognitive and head-related symptoms were not significantly different between the two groups. Notably, for both groups, cognitive symptoms attained the highest mean severity, while the largest inter-group difference occurred for cardiac symptoms. Presumably, cognitive symptoms cause the most difficulty for these respondents. Airway symptoms were significantly more severe for OPs than REs, a finding that was not expected because of the relatively strong association between reports of airway problems and SBS, but not low-level OP exposure.

The finding that pesticide-exposed respondents report similar, but much more severe symptoms than remodeling-exposed respondents is consistent with prior anecdotal observations, and supports the hypothesis that some biological mechanism is operative. If underlying depres-

Table 1 Comparison of Mean (SD) severity of symptom scales in chemical sensitivity exposure groups

Symptom scale	Organo-phosphate	Remodeling	$p <$
Neuromuscular	12.9 (7.5)	9.0 (6.5)	0.007
Head-related	15.9 (7.6)	13.4 (8.3)	0.12
Muscle-related	17.5 (8.8)	14.2 (8.7)	0.06
Affective	17.7 (7.3)	13.0 (6.8)	0.001
Airway	14.9 (7.5)	12.0 (6.5)	0.04
Cognitive	18.0 (8.3)	15.8 (7.7)	0.17
Gastrointestinal	15.3 (7.9)	11.1 (8.4)	0.01
Cardiac	16.5 (8.2)	9.9 (9.0)	0.001
Fifteen most frequent symptoms	20.8 (6.2)	16.7 (6.0)	0.003

sion. somatoform disorder, or other psychological factors were the primary cause of chemical sensitivity, one would expect to see no difference between the OP and RE groups in terms of symptom severity (for a more complete discussion of this point, see Miller and Mitzel 1995). A threat to the validity of these findings remains that of sampling from preexisting groups. a difficulty always present with retrospective studies. For example, the OP group might be over-reporting symptoms relative to the RE group because organophosphate exposure is more specific and involves a known neurotoxin, while the RE group attributes illness to building remodeling, which most people consider benign. In order to explain the findings in this study, such a cognitive hypothesis would require that patients hold powerful beliefs regarding the health impact of pesticide versus remodeling exposures that permeate both their symptom reports and their ideas as to which inhalants and ingestants trigger symptoms. While possible, this explanation seems less parsimonious than the one offered here.

The European investigation

Three teams of investigators recently completed a study of chemical sensitivity in Europe (Ashford et al. 1995). The purpose of their investigation was to explore the existence and nature of chemical sensitivity in nine selected countries. No prior systematic study of the occurrence or magnitude of chemical sensitivity had been undertaken in any European country, and there were no case definitions or agreement on the criteria for diagnosis of the condition. However. it was thought that cross-country studies might yield fresh insights into the problem which appears to be influenced by a number of social and cultural factors. In the United States. where chemical sensitivity has received the most attention. some of these social and cultural factors have. to varying degrees, hindered study and understanding of this problem: Partisan biases among physicians concerning the etiology and relevance of chemical sensitivity: disagreements with respect to who should pay for diagnosis and treatment; chemical manufacturers'

concerns about liability: the presence of well-informed, networked and activated patient groups: and a citizenry with an acute awareness of and concern for environmental exposures. Not all of these factors are present to the same degree in Europe. Therefore, it was felt that a cross-country investigation in Europe might provide a fresh perspective on the subject. as well as afford an opportunity to examine differences between countries in terms of their pattern and use of various chemicals. building construction and ventilation practices and differing traditions of occupational and environmental medicine.

The study was not designed to test any specific hypothesis, but to collect and compare information from several countries that might suggest hypotheses for future research. Definitive conclusions about the nature and etiology of chemical sensitivity were not sought. Following similar protocols, three teams collected data and reported findings: Denmark. Finland. Norway. Sweden. and the United Kingdom (Team A): Belgium. Germany. and the Netherlands (Team B): and Greece (Team C). A computerized literature search was undertaken and persons thought likely to have some knowledge or experience with chemical sensitivity. including ministries of environmental or public health. environmental groups. labor unions, and professional medical associations were contacted and interviewed according to general guidelines. Anecdotal clinical observations and non-peer-reviewed "gray" literature reports were included in the analysis for the additional insights and opportunities they might provide for future study.

Despite the potential usefulness of exposure or event-driven information. the research teams were unable to discover many situations or incidents that could provide useful data relevant to chemical sensitivity as defined above. There is no paucity of events or exposures: there is simply little information available about the outcomes in terms of the development of chemical sensitivity. Information on the temporal features of the development and disappearance/waning of the problems would be very important, but was very difficult to obtain. A variety of factors may explain this relative lack of information. For example, the research tended to focus on physicians and the medical literature as sources of data. In general, physicians interact with individual patients and have little reason (and perhaps interest) to recognize that their patient may be part of a larger group of individuals who have experienced a common exposure or event. Second, physicians. researchers. and health authorities who are involved in events or exposure situations (e.g., a "sick building" or exposures at a particular workplace/occupation) do not likely have a focus on chemical sensitivity and thus have little reason to: (1) follow the affected individuals for long periods of time; (2) identify subsequent sensitivities: or (3) distinguish between initiating and subsequent triggering exposures. Despite this. the research teams did identify some exposure or event-driven information that may be suggestive of low-level chemical sensitivity.

The predominant loci of the alleged initiating exposures/events in this investigation were industrial. office.

Table 2 Some exposures reported as associated with the onset of chemical sensitivity in Europe

Exposure	Denmark	Sweden	Norway	Finland	Germany	Holland	Belgium	U.K.	Greece
Amalgam/mercury		✓	✓		✓	✓			
Anesthetic agents									✓
Carpets and glue		✓				✓			
Diesel exhaust	✓								
Formaldehyde	✓		✓		✓				✓
Hairdressing chemicals	✓	✓							✓
Indoor climate	✓	✓		✓					
Industrial degreasers	✓								
Methyl methacrylate		✓	✓						
New/renovated buildings		✓	✓		✓				
Organic solvents	✓	✓	✓	✓	✓	✓	✓	✓	✓
Paints/lacquers	✓	✓							✓
Pentachlorophenol/wood preservative					✓	✓	✓		
Pesticides	✓		✓		✓		✓	✓	✓
Pharmaceuticals		✓							✓
Printed material	✓	✓							
Stress/psychosocial factors	✓	✓			✓			✓	

and domestic environments. Agricultural exposures resulting in chemical sensitivity were mentioned in several countries. Hairdressers comprised an occupational group that appeared to be affected in several countries.

A relatively small number of substances were specifically associated with the *onset* of chemical sensitivity (Table 2). The substances most often mentioned as initiators included pesticides, solvents, paints and lacquers, and formaldehyde. Repeated or continuous low-level exposure, rather than a single event, characterized most of the experience. Psychosocial stressors were also mentioned as initiating chemical sensitivity.

A unique situation was reported in Germany, where exposure to emissions from treated wood has been associated with its own clinical entity—wood preservative syndrome (or pentachlorophenol syndrome) (Schimmelpfennig 1994). Some individuals exposed to wood (or rooms with wood) treated with pentachlorophenol (PCP) and lindane (contaminated with dioxins and furans, and dissolved in solvents at a concentration of about 5%) have experienced the multitude of symptoms commonly associated with chemical sensitivity. These include immunologic, dermatologic, neurologic, psychiatric, endocrinologic, and ophthalmologic symptoms (Huber et al. 1992). Many of the physicians surveyed in Germany reported that pentachlorophenol and wood preservatives initiated illness and described subsequent sensitivities (e.g., to odors, solvents, and, sometimes, foods) in their patients.

While these investigations were neither exhaustive nor comprehensive, nevertheless, some interesting observations can be made. Pesticides, organic solvents, formaldehyde, and stress were mentioned as causes of chemical sensitivity in many countries, while anesthetic agents were mentioned repeatedly only in Greece. Problems with hairdressing chemicals were mentioned in Denmark, Sweden, and Greece. Of course, the categories "organic sol-

vents" and "pesticides" are overly-broad. Identification of more specific substances in these categories would be more informative. However, in many cases, more definitive information simply was not available. With the exception of pentachlorophenol, these are the same substances associated with the onset of chemical sensitivity in North America (Ashford and Miller 1991).

A much larger number of chemically-diverse substances were reported to trigger symptoms in persons who were already alleged to be chemically sensitive. These parallel the "triggers" frequently reported in the United States and include perfumes, detergents and cleaners, smoke, cooking odors, car exhaust, new clothing, nail polish, newspaper print, etc. Reactions to these substances were reported in each country. Symptoms frequently include: Mucous membrane irritation, gastrointestinal complaints, joint pain, respiratory complaints, such as chest tightness and rhinitis, fatigue, and central nervous system problems, such as headache, dizziness, memory loss, and difficulty with concentration. Physicians reported a higher occurrence of symptoms associated with chemical sensitivity among women in the age group 30–50 in Scandinavia, Germany, and Greece.

Comparison of European and North American experiences with low-level chemical sensitivity

The limited data available at this time from North America and Europe suggest that low-level chemical sensitivity is not a single, distinct clinical entity. Clinical presentations are extraordinarily diverse, a major reason why consensus on a case definition for the illness has been so difficult to achieve despite numerous attempts (Miller 1994a). Symptoms appear to involve any and every organ

system or several systems simultaneously. although central nervous system symptoms such as fatigue. mood changes (irritability, depression). and memory and concentration difficulties predominate. Even among persons who have shared the same initiating exposure. symptoms and severity differ markedly. Ultimately. chemical sensitivity may be more accurately characterized as a class of disorders. like infectious diseases. which share a common general mechanism. yet within the class. particular members may involve different symptoms. agents. and specific mechanisms.

From European and North American observations. a wide range of environmental exposures appear able to initiate the problem. While implicated chemicals are structurally diverse. certain ones appear again and again on both continents:

1. Pesticides are frequently cited in North America and Europe. with the exception of Sweden. Finland, and the Netherlands, where indoor use of pesticides may be less frequent as a consequence of cooler temperatures and reduced insect populations. Organophosphate and carbamate pesticides are those most often reported as causing illness in the United States, but this may simply reflect the fact that these are among the agents most commonly applied. The greater symptom severity reported by chemical sensitivity patients exposed to organophosphates versus remodeling, summarized earlier in this paper, suggests that some compounds in this class might be especially potent sensitizers, at least for a subset of the population.

2. Organic solvent exposure was cited in every European country surveyed and is commonly cited in North America. Such exposures frequently occur in the workplace and are more often chronic than acute in nature.

While there are consistent observations regarding causes of chemical sensitivity between continents. there are also notable differences. for example. the so-called "wood preservative syndrome" associated with pentachlorophenol use in Germany.

Although SBS is widely recognized in the Scandinavian countries where a number of internationally-known researchers are engaged in its study, instances of sick building syndrome per se did not generally reveal chemically sensitive subgroups. Conceivably. preoccupation with immediate effects may have obscured their discovery. Certainly, there was no indication of a large problem in those instances. Initiating experiences with carpets were noted, however. If future inquiry were to reveal that chemical sensitivity does not occur in even a subset of individuals in European SBS episodes, this finding might suggest the importance of other factors. for example. the use of wall-to-wall carpeting (common in the United States and relatively infrequent in Europe). or use of certain fragrances, air fresheners. cleaners. and/or extermination practices.

In both Europe and North America. patients report spreading of their sensitivities to an array of common exposures, including fragrances. cleaning agents. engine exhaust, alcoholic beverages. foods. and medications the formerly tolerated without difficulty. The fact that mar of these individuals voluntarily forego pizza. chocolat beer. or other favorite foods because they make them fe so ill warrants consideration − there is little secondar gain to be garnered from such forbearance. Many partic pants in the North American study reported that drugs. ir gestants containing chemical additives (monosodium glt tamate. chlorinated tap water). and food-drug combina tions (alcoholic beverages or xanthine-containing foods made them ill. a finding consistent with a hypothesis tha these individuals exhibit amplified responses to pharma cologic doses of a variety of substances (Bell et al. 1992)

Generally speaking. awareness of chemical sensitivity may be greater in countries with more environmental ac tivism. but illnesses resembling chemical sensitivity were described in every country that was studied. Clinical ecol ogy's origins in the United States and its spread to othei English-speaking nations, including Canada and the United Kingdom. no doubt have influenced the numbers of patients receiving a diagnosis of chemical sensitivity in those countries. Discord among physicians as to what constitutes appropriate diagnostic and therapeutic approaches in these countries permeates professional meetings. medical journals. and court proceedings. Where patients must "prove" a particular exposure caused their illness in order to receive worker's compensation or reimbursement for medical expenses (as in the United States where there is no national health care system). disputes between medical practitioners (who may testify on opposing sides) are most contentious.

Cultural practices may affect the prevalence of chemical sensitivity. In some European countries. people typically spend several hours each day out-of-doors. for example. walking to work or shopping, and windows in homes and offices may be left open part or most of the day. In contrast. on average. Americans spend 90% or more of the day indoors. often in tightly-sealed structures. where levels of certain volatile organic air contaminants can be orders of magnitude higher than out-of-doors.

Choices of building construction materials and furnishings also vary greatly between countries, including use of wall-to-wall carpeting versus washable throw rugs or no floor coverings at all: solid hardwood furnishings versus particle board or pressed wood: paint. wallpaper. and adhesive constituents: office equipment, including photocopiers and computers. etc.

Ventilation practices may be similarly diverse. Tightly-constructed buildings with little fresh make-up air built in North America since the oil embargo of the mid 1970's could be a factor that explains the apparent increase in chemical sensitivity cases over the past two decades in the United States and Canada. The experience with SBS. but not chemical sensitivity. in Scandinavia merits closer examination to determine whether the latter condition has thus far escaped attention or whether environmental or perhaps genetic or cultural differences may prevent development of the condition.

Use of chemicals also varies from country to country, in particular, pesticides, cleaners, and personal care products, including fragrances. Comparing differing rates of consumption of these products, as well as pharmaceuticals, and the incidence of chemical sensitivity among countries, could provide further clues.

Conclusion

Complex questions concerning the origins and mechanisms of chemical sensitivity will not be resolved by retrospective survey studies, indeed, probably not by retrospective studies of any kind. Perhaps more informative would be prospective observations on the natural history of chemical sensitivity associated with particular incidents or exposure events rather than isolated case reports. Nevertheless, enlightening similarities and instructive differences can be gleaned from future, more directed cross-country comparisons of experiences with chemical sensitivity.

In the past five years in the United States, controversies surrounding chemical sensitivity have exploded far beyond the narrow confines of a medical debate into a national debate with far-reaching policy and regulatory implications. Most recently, a number of U.S. Persian Gulf veterans have reported multi-system health problems and new-onset intolerances to chemicals, foods, and other substances since returning from the war (Miller 1994b). Some have received a diagnosis of chemical sensitivity from private physicians and now seek medical care and compensation for the condition. Such trends in North America could be mirrored in European countries over the next few decades.

Understanding chemical sensitivity is pivotal to establishing sound environmental policy. If there is a subset of the population that is (or can become) especially sensitive to low-level chemical exposures, a strategy for protecting this subset must be found. If it were to be determined that certain chemical exposures can lead to sensitization, then perhaps these exposures could be avoided. Perhaps by preventing chemical accidents, prohibiting occupancy of buildings prior to finish-out or completion, avoiding use of certain cholinesterase-inhibiting pesticides indoors, etc., society could protect more vulnerable individuals from becoming sensitized in the first place. It would make little sense to regulate chemicals at the parts per billion level or lower if what was required was to keep people from becoming sensitized in the first place. Indeed, by understanding the true nature of chemical sensitivity and who is at risk, we may prevent unnecessary and costly overregulation of environmental exposures in the years to come.

Chemical sensitivity could be a new paradigm that has the potential to explain many chronic and costly illnesses, including fatigue, depression, headaches, and asthma, or it could continue to elude definition. Not understanding chemical sensitivity, we take an immense gamble. But knowledge will not come cheaply. Future studies on chemical sensitivity that involve blinded challenges in a controlled environment, that utilize brain imaging, state-of-the-art immunological testing or other sophisticated tests, and that compare adequate numbers of patients and controls, will be costly. Funding agencies will need to invest adequate sums to acquire answers in this area as they have for other diseases, such as breast cancer and AIDS. Until sufficient research funds become available, chemical sensitivity no doubt will continue to pit physician against physician, perplex policy makers, and impoverish patients and corporations alike.

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