

DOES PB LEAD TO MCS?

Multiple chemical sensitivity (MCS) is a putative condition without a widely accepted clinical case definition, in which persons report new subjective sensitivity to low-level exposures to multiple chemicals and foods, typically following a (self-reported) environmental exposure to pesticides, organic solvents, or building remodeling. The condition has also recently been termed “toxicant-induced loss of tolerance” (TILT) (Miller, 1997; Miller, Ashford, et al., 1997). Symptoms referable to multiple organ systems are reported by subjects with MCS; these include ear-nose-and-throat, CNS, GI, genitourinary, skin, and musculoskeletal symptoms, among others (Davidoff and Keyl, 1996; Miller and Mitzel, 1995).

Many ill veterans report new intolerances to chemicals (Gordon 1997), and some studies are underway to further assess chemical sensitivity in ill PGW veterans (Fiedler, Kipen, et al., 1996).

The lack of a clinical case definition for either MCS or illnesses in PGW veterans complicates examination of a connection between these two phenomena. Nonetheless, several factors are consistent with a connection between illnesses in some PGW veterans, and “toxicant-induced loss of tolerance,” or MCS. Similar exposures, namely to acetylcholinesterase-inhibiting agents, characterize ill PGW veterans and many MCS patients. Some work is beginning to *suggest* mechanisms by which cholinergic exposures, experienced by some PGW veterans, could induce chemical sensitivity. These mechanisms include partial kindling of the limbic system and alteration of nasopharyngeal mucosal function. Studies have found that similar EEG abnormalities may characterize persons with selected AChE inhibition exposures seen during the PGW (sarin, OP pesticides) and persons with MCS, though it has not been shown that ill PGW veterans with consistent symptoms share these EEG abnormalities (neither has it been shown that they do not). SPECT studies (single photon emission com-

puterized tomography, which evaluates regional cerebral blood flow) in a small segment of PGW veterans with chemical sensitivities have reportedly been abnormal, as have SPECT scans in individuals exposed to pesticides (see Chapter Fourteen, "Chronic Effects"), although larger samples of all veterans and controls should be evaluated using blinded testing. At present, it is premature to accept a connection between illnesses in PGW veterans and MCS; however, it is premature to reject the possibility of such a connection. Further study is warranted. The following text explores these issues in greater detail.

MCS CASE DEFINITION

While no case definition is universally accepted, several attempts at a case definition for MCS have been made (See review in Miller, 1994). According to one researcher, "MCS is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms" (Cullen, 1987). Although exposures that produce symptoms are far below legal exposure levels, it has been stated that no-effect levels for chemical exposures from chronic animal studies are often orders of magnitude below current legal exposure limits (Ziem, 1992). Another researcher suggests five criteria for MCS: Symptoms are reproducible with exposure; condition is chronic; low levels of exposure result in manifestations of the syndrome; symptoms resolve with removal of the incitants; and responses occur to multiple chemically unrelated substances (Nethercott, Davidoff et al., 1993).

MCS ETIOLOGY

No objective correlate has been identified for MCS. Not surprisingly, then, many theories of causation have been advanced (Rest, 1992), including immune dysfunction (Levin and Byers, 1992; Albright and Goldstein, 1992) (not confirmed, see Simon, Daniell, et al., 1993), respiratory epithelium dysfunction (Bascom, 1992), behavioral or biological conditioning (see "Limbic Kindling," below), psychiatric illness (Staudenmayer, Selner, et al., 1993; Gots, Hamoosh, et al., 1993) and cultural suggestion or "overvalued beliefs" (Staudenmayer, Selner, et al., 1993). For a cogent review of some of these theories, see Sparks, et al. (1994). The present text will concentrate on theories and mechanisms that may relate use of PB and other PGW exposures to development of an MCS-like condition.

MCS AND ILLNESSES IN PGW VETERANS

MCS and illnesses in PGW veterans have several characteristics in common, some of which support a comparison whereas others complicate it.

For each condition, the following is true:

- There is no clear case definition.
- There are no identified objective measures that distinguish persons with and without the condition.
- Persons with a common or similar (self-reported) exposure report common or similar subsequent symptoms of debilitating disease. In the case of MCS, typical AChE-inhibiting OPs or carbamate exposures are to pesticides, solvents, or remodeled buildings (with presumed mixed solvent exposures); organic solvents have been shown to inhibit AChE in vitro (Korpela and Tahti, 1986; Korpela, Tahti, et al., 1986). For PGW veterans AChE-inhibiting exposures that may have attended Gulf War participation include PB, pesticides, and low-level nerve agents. (Again, current modeling efforts supported by DoD estimate that over a three-day period up to 100,000 U.S. veterans, as a result of allied forces destruction of an Iraqi ammunitions depot at Khamisiyah, may have been exposed to levels of sarin and cyclosarin above the general population limit—the level presumed safe for indefinite exposure—but below the level at which first symptoms would be identified (Gulflink, 1997))—although this estimate is likely high.
- Chronic multisystem complaints follow the exposure.
- Many persons with apparently similar exposures fail to report similar symptoms of disease.
- Patients, as well as some physicians and researchers, are firmly convinced the condition is organic. Other physicians and researchers believe the origin is psychological.

Because the MCS condition is itself not well understood or even universally accepted, this condition is poorly positioned to serve as an “explanation” of illnesses in PGW veterans. Nonetheless, parallels between these conditions may allow cross-fertilization of ideas in exploration of the cause of illness in persons labeled with each of the two conditions.

This chapter will consider the following topics: parallels in exposures and symptoms in ill PGW veterans and patients with MCS; incidence of chemical sensitivities in PGW veterans; results of a SPECT study in a sample of PGW veterans with chemical sensitivities; and points of contact between MCS and PB.

Parallels in Exposures and Symptoms in Ill PGW Veterans and in MCS

Many patients with MCS and ill PGW veterans have in common prior exposures to AChE-inhibiting agents. Subgroups of MCS patients have self-reported exposures to carbamate or OP pesticides or chlorpyrifos (Ziem, 1997), to solvents in industry, or to mixed solvents associated with building remodeling. Carbamate and OP pesticides are AChE inhibitors, and, as previously noted, organic solvents have been shown to inhibit AChE in vitro (Korpela and Tahti, 1986; Korpela, Tahti, et al., 1986). Many PGW veterans experienced exposures to PB, to low levels of nerve agents, pesticides, and solvents, as well as oil fires, vaccines, and perhaps infectious disease.

MCS and PGW patients both report prominent alterations in concentration and memory (Miller, 1994; Fukuda, Nisenbaum, et al., 1998; Iowa Persian Gulf Study Group, 1997). Moreover, MCS and PGW subjects share other categories of symptoms, including musculoskeletal, respiratory, and dermatological. Moreover, as previously mentioned, many ill PGW veterans report new chemical sensitivities (Gordon, 1997).

The ten most frequent complaints of PGW veterans enrolled in the Persian Gulf Health Registry with complaint data available are shown in Table 11.1. Symptoms in MCS patients are shown in Table 11.2. These tables are not directly comparable because the mode of questioning influences the symptoms reported. Nonetheless, both lists share fatigue (systemic complaints), headache,

Table 11.1
Complaints of PGW Veterans Enrolled in Persian Gulf Health Registry (%)

Complaint	Men	Women
Fatigue	23.3	20.7
Headache	23.0	17.7
Skin rash	18.2	18.5
Muscle or joint pain	14.5	16.5
Loss of memory or "other general symptoms"	13.9	14.2
Shortness of breath	7.6	8.0
Sleep disturbances	5.3	5.9
Abdominal pain	3.9	2.5
Other symptoms involving skin and integument	3.8	3.2
Diarrhea and other GI symptoms	3.6	4.5

SOURCES: IOM report (Committee to Review the Health Consequences of Service During the Persian Gulf War; IOM, 1996); Persian Gulf Health Registry data provided to IOM Committee to Review the Health Consequences of Service During the Persian Gulf War.

Table 11.2
Symptoms in MCS Patients

Symptom	Percentage ^a
Ear-nose-throat	90–100
GI	40–95
Systemic	60–90
Musculoskeletal	80–100
CNS, excluding headache	80–85
Headache	65–100
Dermatologic	60–80
Lower respiratory	75–100
Genitourinary	20–65
Circulatory	25–80

^aPercentage ranges reflect prevalence for four MCS subgroups.

SOURCE: Miller and Mitzel, 1995; Davidoff and Keyl, 1996.

skin rash, musculoskeletal complaints, CNS complaints, GI complaints, and respiratory complaints. But ear, nose and throat symptoms, sleep disturbances (unless that is included in systemic complaints), genitourinary, and circulatory symptoms are distinct. MCS subjects report higher levels of these complaints—a difference that could reflect true differences in subjective symptom patterns, differences in exposure levels, or differences in referral and self-referral patterns for the two conditions. Moreover, both similarities and discrepancies in listed symptoms could be artifacts of the methods of questioning. Indeed, one investigator reported, in testimony, quite similar rates of various symptoms in ill PGW veterans and MCS subjects, presumably employing a common mode of questioning (Miller, 1996b). However, these findings have not been published in a peer-reviewed source.

EEG abnormalities have been reported in MCS subjects (Miller, 1992) and in persons exposed to AChE inhibitors, such as OPs (Duffy, Burchfiel, et al., 1979; Duffy and Burchfiel, 1980). (Such changes include increased beta and decreased alpha activity.) How similar these changes are in those with different exposures, and whether the EEG changes seen in pesticide-exposed persons with MCS also occur in ill Gulf War veterans with PB exposure, is unknown.

Incidence of Chemical Sensitivities in PGW Veterans

No peer-reviewed data are available regarding the incidence of new chemical sensitivities in PGW veterans. Testimony from many veterans has included comments about new sensitivities to foods, cigarettes, alcohol, and chemicals (Subcommittee on Human Resources, 1997a, 1997b), and in one report, many of 549 PGW veterans evaluated reported “high intolerance” to chemicals in the

environment (Gordon, 1997). Moreover, according to evidence presented in testimony, of 59 consecutive PGW veterans seen at the Houston VAMC Regional Referral Center, 78 percent reported new intolerances (Miller, 1996b) (see Table 11.3).¹ While this analysis is severely limited by the absence of a control population, it does suggest possible development of new chemical and food sensitivities in some ill PGW veterans, at a rate that may exceed that in the general population. Consequently, it favors efforts to examine PGW illnesses in the context of efforts to study putative MCS.

SPECT Study in PGW Veterans with Chemical Sensitivities

One small study (six cases, six controls) performed SPECT scanning (a method for looking at regional cerebral blood flow) on six male PGW veterans “with chemical sensitivities” and six controls reportedly determined not to have toxic exposures. Abnormalities were reported in all six SPECT reports from PGW veterans with sensitivities (abnormalities were classified as mild in one, moderate in two, and severe in three), while all six reports from controls were read as normal. Soft tissue diversion was noted in three cases (but no controls), lobar discrepancies in three cases (and one control), focal findings in five cases (and one control), and phase mismatching in four cases (and one control). Findings in all PGW veterans were noted to be similar to those seen in patients with

Table 11.3
New Onset Intolerances Reported by Gulf War
Veterans: n = 59 Veterans Seen at Houston
VAMC Regional Referral Center

Food or Chemical	Percentage with New Intolerances
Chemical inhalants	78
Medications	40% of those taking drugs
Alcohol	66% of alcohol users
Caffeine	25% of caffeine users
Tobacco use	74
Foods	78
Specific foods	64
Illness after meals	49

SOURCE: Non-peer reviewed testimony (Miller, 1996b).

¹Anecdotal stories from some PGW veterans suggested striking changes in sensitivity: One veteran reported that his idea of the perfect perfume had been WD-40, whereas since the PGW that and many other low-level chemical exposures made him feel ill. Other mechanics stated they used to “bathe” in solvents, or enjoy the smell of engine exhaust before the war, while afterwards they reported severe symptoms with these exposures (Miller, 1996b).

known exposure to widely recognized neurotoxins “including petroleum distillates and pesticides” (Simon, Hickey, et al., 1994). (Indeed, qualitative and quantitative SPECT performed on patients with OP pesticide and solvent exposures have demonstrated abnormalities despite nondiagnostic MRI brain scans—abnormalities that are reportedly distinct from the findings seen with depression and “late-life chronic fatigue syndrome.” (Heuser, Mena, et al., 1994).) SPECT is regarded by some as a “sensitive and potent” indicator of CNS function impairment after neurotoxic exposure (Heuser, Mena, et al., 1994). However, specificity remains an issue, because SPECT abnormalities may occur in many conditions, including depression. Of note, it has been suggested that focal cortical hypoperfusion with limited temporal lobe involvement may suggest a direct cortical effect of neurotoxins, rather than a limbic effect suggested in the kindling hypothesis.

The reported SPECT findings in PGW veterans may have important implications if they can be replicated in a larger, more carefully controlled study, but the present study has significant limitations. The sample was extremely small; subject selection procedures, including criteria for “chemical sensitivity,” were not clearly delineated; the SPECT readings were qualitative and not stated to be blinded; no primary outcome variable was identified; and no statistics were offered. Moreover, results in all veterans with chemical sensitivities might not be reflective of results in other ill veterans; the estimate of 78 percent of ill veterans with new sensitivities, cited previously, might not reflect values in larger samples of veterans or ill veterans, and criteria for chemical sensitivity may differ from those in the present study. Therefore, these findings, while intriguing, must be viewed as preliminary. Nonetheless, attempts should be made to replicate the finding of SPECT abnormalities in the form of focal hypoperfusion and to extend this work by ascertaining if these defects are selectively enhanced when patients are symptomatic following reexposure to an offending chemical, to determine whether SPECT scanning could offer a much needed, if costly, objective marker for chemical sensitivity.

Points of Contact Between MCS and PB

Because a clinical case definition has not been accepted for either MCS or PGW illnesses, any discussion of common etiology must be regarded as hypothesis-generating rather than hypothesis-supporting. Nonetheless, there are points of contact between cholinergic function (which is influenced by PB) and the putative MCS syndrome, and these points of contact merit review:

1. **AChE Inhibitor Exposure:** Several defined MCS subgroups have self-reported exposure to AChE inhibitors. Exposure to OP or carbamate pesticides (all AChE inhibitors) reportedly produces particularly severe MCS

symptoms. Exposure to organic solvents (shown in vitro to inhibit AChE (Korpela and Tahti, 1986; Korpela, Tahti, et al., 1986)) is also reportedly linked to MCS; and exposure to recent building remodeling (or “tight buildings”) has been postulated to occur through solvent exposure.

At least 250,000 PGW veterans were exposed to AChE inhibition through PB. An estimated 100,000 may have been exposed to low levels of nerve agent following the demolition of the Iraqi Khamisiyah ammunitions depot (Gulflink, 1997), and many additional veterans were exposed to pesticides, solvents, and petroleum products. Thus, AChE exposure is common to many PGW veterans and to many or most MCS subjects.

2. **Cholinergic hypothesis:** It has been reported that reduced AChE parallels the increase in hypersensitivity to stimuli (Girgis, 1986), that the limbic system is especially rich in AChE, and that AChE may play a protective role by maintaining ACh concentrations within safe bounds and protecting susceptible limbic neurons from developing “bizarre sensitivity” (see “Limbic Kindling,” below). Indeed, AChE inhibitors including OP pesticides and organic solvents (from industrial exposure or exposure following building remodeling) are common reported “incitants” of putative MCS. If this cholinergic hypothesis is correct, then administration of PB during stress (leading to PB crossing the blood-brain barrier), or administration of PB in concert with exposure to AChE inhibitors that cross the blood-brain barrier, could promote heightened susceptibility to chemical sensitivities. At present this is speculative.
3. **Nasopharyngeal factors and the respiratory mucosa:** The airway epithelium (the outermost layer of cells that make up the “mucosa” or lining of the respiratory tract) and the fluid it produces and regulates are the first line of defense against constituents in the air inhaled each day; moreover, the nasal cavity contains enzymes that help to metabolize foreign substances (Bascom, 1992). It has been suggested that patients with MCS have altered function of the respiratory mucosa (Sparks, Daniell, et al., 1994; Bascom, 1992), perhaps through alteration of “c-fiber neurons,”² altered function of the respiratory epithelium per se, or an altered interaction between the nerve cells and the epithelium (Bascom, 1992). Increased vascular permeability of the respiratory tract has occurred with some chemical irritants, through activation of the c-fiber neurons (Bascom, 1992); and certain “cytokines” (another form of chemical signal in the body involved in such functions as inflammation) are released by epithelial cells in response to

²C-fiber neurons are nerve cells that branch extensively in the mucosa and contain neuropeptides, or small proteins that serve to convey signals, such as “vasoactive intestinal peptide,” “substance P,” which is involved in perception of pain and production of inflammation, and calcitonin gene-related peptide.

chemical exposures. Moreover, some alteration in properties of the mucosa in MCS patients is indicated by the finding that these individuals have increased nasal resistance (Doty et al., 1988).³ Study of airway epithelial “neutral endopeptidase” has been suggested, as reduction in this enzyme could result in amplified response to subsequent c-fiber stimulation by other inhaled irritants (Bascom, 1992).

In one study, 10 of 10 MCS subjects were found to have abnormal rhinolaryngoscopic findings including edema, excess mucus, “cobblestoning” (an alteration in the appearance of the mucosa), mucosal injection (redness of the mucosa from surface capillaries), and blanching around vessels (Meggs and Cleveland, 1993). However, there were no controls and no blinding in evaluation.

A relation to PB could conceivably occur, since cholinergic function is involved in nasopharyngeal mucociliary action (Sastry and Sadavongvivad, 1979). Therefore dysregulation of cholinergic function (which may be influenced by PB alone or in concert with other exposures influencing the cholinergic system) could prolong nasal exposure to chemicals and perhaps participate in altering nasal resistance and contributing to symptoms. As a related or independent mechanism, some lipophilic pesticides and other agents could partition into membranes of the respiratory mucosa, altering their properties (Moya-Quiles, Munoz-Delgado, et al., 1995).⁴ This mechanism would not require central exposure to AChE inhibition.

4. EEG abnormalities: EEGs from 58 “universal reactors” (MCS patients) were compared with EEGs from 55 healthy controls. The MCS positives were shown to have evidence of increased beta and reduced alpha activity (Staudenmayer, 1990), similar to EEG abnormalities demonstrated following exposure to AChE inhibitors, including OP pesticide or sarin (Duffy, Burchfiel, et al., 1979; Duffy and Burchfiel, 1980). PB is an AChE inhibitor and may also potentiate the effects of other AChE inhibitors (see “Interactions”); one could speculate that PB could contribute to development of EEG abnormalities in some PGW veterans. Some studies have reported EEGs to be “normal” in PGW veterans. Others maintain that specific abnormalities are present and must be specifically sought, but have

³One cross-sectional survey, cited in a review only as “personal communication,” reportedly found a relationship between self-reported mucosal symptoms in the workplace, such as eye, nose, throat, and respiratory irritation, and self-described heightened chemical sensitivity to such workplace elements as tobacco, fumes from a photocopying machine, new carpet, pesticides, new furniture, or paint (Bascom, 1994).

⁴Of anecdotal interest, some patients with self-described chemical sensitivities report noticeable symptom abatement with behaviors that increase salivation such as chewing gum; however, abatement of symptoms through this means does not necessarily imply that the pathology involved is nasopharyngeal.

not been examined in published negative studies (Baumsweiger, 1998). Blinded studies involving sleep and waking EEGs in ill PGW veterans and matched controls, including examination of beta activity, are currently under way (Haley, 1998, citing work with R. Armitage and R. Hoffman).

LIMBIC KINDLING: ONE PROPOSED MECHANISM FOR MCS

Kindling refers to a condition in which potent or repeated electrical or chemical stimuli permanently augment the tendency for neurons to “fire” (send a signal) in response to future excitatory inputs, even in response to much lower level signals than those originally involved. The amygdala, an area of the brain involved in emotion and aversive conditioning, is particularly susceptible to kindling, as are the olfactory pathways (Sato, Racine, et al., 1990).

Animal studies suggest that priming an animal with high or repeated concentrations of any of various chemicals, including pesticides (Bell, Miller, et al., 1992), and subsequently reexposing the animal to low concentrations of the same or different chemicals may produce increased likelihood of paroxysmal electrical discharge in the amygdala. Though the agents used to sensitize animals may differ chemically, the effects on the limbic system are quite similar. Bokina (1976) has suggested that these findings parallel clinical observations in MCS and that kindling could amplify reactivity to low-level inhaled and ingested chemicals and initiate persistent affective, cognitive, and somatic symptomatology (Bell, Miller, et al., 1992). Partial kindling (kindling leading to levels of paroxysmal electrical discharge below those resulting in seizure activity) has been shown to increase avoidant behavior in animals, including cats (Bell, Schwartz, et al., 1993a). One could speculate that MCS results from entrainment of strong aversive signaling in response to chemical exposures. (Of note, vagal stimulation has been approved by the FDA for treatment for intractable partial seizures (Zoler, 1998), potentially consistent with a connection between the ACh system and seizures, but the nature of the relationship remains confusing.)

The amygdala is closely connected to the hippocampus, another brain area involved in limbic functioning that is also felt to play an important role in learning and memory (in which many MCS and PGW subjects report impairments). Hippocampal damage may affect production, storage, or release of excitatory and inhibitory neurotransmitters, and small perturbations in hippocampal function can have lasting effects on behavior and cognition. The hypothalamus, part of the brain with rich limbic input that controls many autonomic and somatic functions, has also been postulated to play a role in development of symptoms in patients with subjective sensitivities (Miller, 1992).

Factors that lower the seizure threshold (that is, factors that facilitate the development of seizures in response to potentially seizure-producing stimuli), such as estrogen in women, might be expected to facilitate kindling sensitization (Bell, Schwartz, et al., 1993a).⁵

Indeed, studies in rats have found a greater susceptibility to sensitization in female than male rats (Antelman, 1988); and sex differences have been found for other, analogous neuronal effects (such as long-term facilitation following a single exposure to amphetamine) (Robinson, Becker, et al., 1982). This finding may have a clinical correlation in that predominantly females report symptoms of MCS (Miller and Mitzel, 1995), though the MCS cases that follow certain incitants are more commonly male (such as exposure to industrial solvents), reflecting the predominantly male group that is exposed. Self-reported illness from foods and chemicals in young adults (ascertained with no attempt to meet MCS “criteria”) also occurs predominantly in females (Bell, Schwartz, et al., 1993b). Meanwhile, although 93 percent of PGW veterans were male, and while there may be a slight trend toward higher reported incidences of symptoms in female veterans, differences, if any, are not marked. Among those veterans in the VA Persian Gulf Health Registry, 69 percent of women reported their health as all right, good, or very good compared with 73 percent of men (Committee to Review the Health Consequences of Service During the Persian Gulf War; IOM, 1996). These subjects were self-selected to participate in the registry, and the generalizability to all PGW veterans is uncertain. (Of note, exposures for male and female veterans may have differed. If male veterans experienced more exposures than females, then symptom rates may underrepresent differences in response to exposures. No data regarding differences in exposures between males and females have been identified.)

INDIVIDUAL DIFFERENCES AND INTERACTIONS

Self-reported chemical sensitivities following exposures to pesticides, solvents, or building remodeling affect some but not all exposed persons. Since there are no experimental dose-response studies (and perhaps such studies cannot be

⁵Consistent with the identified effect of estrogen on seizures in animals, recent studies in humans have found that epileptic women have fewer seizures after menopause, and hormone replacement treatment may worsen seizures (Harden, 1997). The effect of estrogen on enhancing ACh function or action is suggested by postmenopausal estrogen’s ability to delay onset of dementia (Jacobs, Tang, et al., 1998)—Alzheimer’s-type dementia involves ACh dysfunction and is treated by drugs that increase ACh action. However, complicating the question of how ACh influences seizures, evidence has recently shown that stimulation of the vagus nerve—which produces ACh action in the periphery—has been shown to significantly reduce the number of seizures (Handforth, 1998). Of incidental note, headache may occur as a pre-seizure event (French 1997), suggesting a possible role for increased ACh action in some headaches. Headaches are a prominent symptom in many ill PGW veterans.

ethically performed), it cannot be established whether the fraction of persons affected varies smoothly with degree of exposure to an agent. No organic markers have been identified to predict which subjects will be affected, and no organic markers are known that correlate strongly with who reports subjective symptoms. Some small studies report alterations in lymphocyte subsets, activated T lymphocytes, or autoimmune antibodies; however, these differences require replication and are of unknown significance (Miller, 1992).

Genetic polymorphism and quantitative variability in many enzymes involved in detoxification of xenobiotics offer a possible mechanism by which individual differences in susceptibility could be examined (see Chapter Eight, "Individual Differences in Reactions to PB"). Moreover, interactions with other drugs, exposures, or stresses may influence the effective dose received by an individual (see Chapter Nine, "Interactions Between PB and Other Exposures"). Interactions between chemicals may produce an effect in other ways, perhaps by targeting the same or different elements of the nervous system. It has been observed that less than 10 percent of the 70,000 commercially available chemicals have been evaluated for neurotoxicity. Furthermore, data regarding effects of such chemicals are almost universally deficient in information about chronic or long-latency effects (Landrigan, Graham, et al., 1994).

INTERACTIONS AND TIME-DEPENDENT SENSITIZATION

A putative phenomenon termed "time-dependent sensitization" refers to the progressive amplification of behavioral, neurochemical, hormonal, and/or immunological responses to a single or to multiple exposures to an exogenous agent (Antelman, Eichler, et al., 1980; Antelman, 1988; Antelman, Knopf, et al., 1988; Antelman, Kocan, et al., 1992). It has been reported that nonpharmacological stress can accentuate pharmacological kindling (Cain and Corcoran, 1985) and that the hypothalamic stress hormone, CRF, can facilitate the acquisition of sensitization and kindling while CRF antagonists may inhibit development of sensitization (Karler, Finnegan, et al., 1993). (Of note: the amygdala and hippocampus, noted earlier to be key participants in the limbic system, are the brain areas with greatest density of receptors for corticosteroids.) Additional work must be done to confirm these observations. Moreover, the relevance of these observations to MCS and to illnesses in PGW veterans remains to be defined.

PSYCHOSOMATIC VERSUS ORGANIC DISEASE: ONE PERSPECTIVE

For both MCS and illnesses in PGW veterans, there is active debate about the relative roles of psychological and organic factors.

Cacosmia (abnormal perception of smells as bad) is found to be at best weakly related to such psychological variables as trait shyness ($r = 0.18$), anxiety ($r = 0.08$), and depression ($r = 0.16$) (Bell, Schwartz, et al., 1993b). Moreover, MCS subjects do not differ significantly from controls in factors thought to predict psychiatric illness, such as family psychiatric history, treatment of a psychiatric condition not linked to illness, or unusually intense or long-lasting stress during childhood (Davidoff and Keyl, 1996). Though overall psychiatric symptoms are greater in MCS patients than in controls (correlating significantly with the presence of illness) (Simon, Daniell, et al., 1993; Davidoff and Keyl, 1996), this may reflect effect rather than cause. Similar studies could profitably be undertaken in PGW veterans: a negative result in a well-designed study would reduce the likelihood that illness is of “psychological” origin. A positive result would not necessarily discriminate between organic and “psychological” origin.

It must be remembered that some mood disorders (for instance) are linked to abnormalities in ACh system function. Persons with altered ACh function could have different susceptibility to effects from drugs like PB that act on the ACh system: thus, if a relation between development of illnesses in PGW veterans and prior mood disorder (or other conditions known to be associated with altered ACh function) were found, this would not necessarily imply increased likelihood of a “psychosomatic” origin to disease (if such a concept has any meaning at all); rather, if susceptibility to illnesses in PGW veterans is found to be differential according to psychiatric predisposing factors and existing conditions, the relevant neurochemistry of those conditions should be assessed for clues to the biological basis of illnesses in PGW veterans (see Chapter Thirteen, “Neurotransmitter Dysregulation”).

Several observations have been cited to suggest that MCS and illnesses in PGW veterans could have an organic basis. These include the following:

- The groups reporting similar symptoms and intolerances following an exposure event are demographically diverse (Miller, 1996b).
- Temporal cohesiveness exists between the onset of multiple intolerances and an exposure event (Miller, 1996a and 1996b). (In fact, temporal cohesiveness is present in at best a loose sense in ill PGW veterans; for many, symptoms began significantly after PGW exposures.)
- There is internal consistency in these patients’ reporting not only intolerances to common airborne chemicals, but also to various foods, drugs, caffeine, and alcoholic beverages (Miller, 1996b).
- Many MCS patients who have avoided problem chemicals and foods report marked improvement or resolution of their symptoms (Miller, 1996b).

- Psychological “overlay” occurs in many chronic illnesses such as diabetes, atherosclerotic heart disease, or lupus; presence, if any, of psychological symptoms is a common consequence of illness and in no way precludes an organic cause (Levin and Byers, 1992).

Labeling either MCS or illnesses in PGW veterans as psychogenic or as primarily stress-related is both unsubstantiated and potentially counterproductive. At present, no solid evidence indicates that illness in either MCS patients or in PGW veterans is psychogenic; rather, the cause of symptoms is unknown.⁶

METHODS OF STUDY

Blinded attempts to replicate MCS symptoms following selective exposures have not been successful (Staudenmayer, Selner, et al., 1993), but testing strategies used have been criticized. Improved empirical approaches to the study of MCS have been suggested. These recommend using carefully controlled double-blind testing, employing people of a similar background, and in particular they recommend a period of “unmasking” (Miller, 1992, 1997; Miller, Ashford, et al., 1997) involving an expensive Environmental Medical Unit. Unmasking entails removing the subject from interfering exposures for a period so the effect of a target exposure can be identified, isolated from interfering recent exposures. This method sounds promising but would be expensive and fraught with difficulty. (How can subjects be challenged without infringing on the environmental properties of the proposed unit? How can one be certain that potentially problematic exposures have been extinguished from the unit? How can one “blind” chemicals with identifiable smells, since addition of a “blinding” smell may block olfactory receptors required for action of the exposure?) Moreover, unmasking has yet to be validated as a technique for discriminating subjects who report and who fail to report symptoms of sensitivity to multiple chemicals or for distinguishing chemicals to which subjects are and are not sensitive. Nonetheless, if obvious problems can be overcome, such a unit might be useful in demonstrating or refuting blinded reproducibility of MCS symptoms in response to selected exposure in MCS patients and PGW veterans who report new sensitivities. This may provide a basis for objective testing for MCS that could be a foundation for future research.

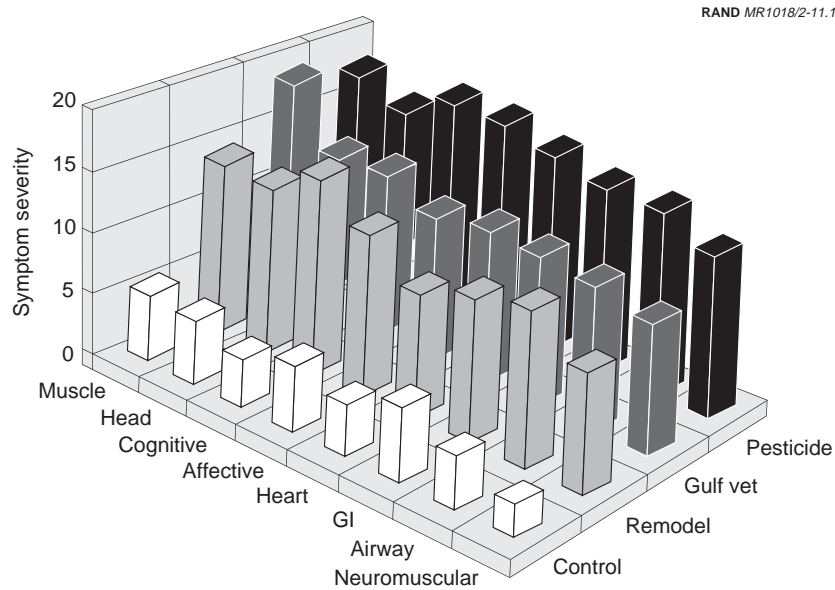
⁶Distress at being labeled with psychogenic illness has been voiced by both MCS patients (Miller, 1994) and by PGW veterans (Subcommittee on Human Resources, 1997a, 1997b; Zeller, 1997). Such characterizations have engendered alienation among veterans, who have referred to them as degrading and have correctly described them as unfounded (Sumpter-Loebig, 1997).

QUANTITATIVE VALIDATION

MCS remains to be uniformly accepted as a medical condition. Nonetheless, two studies have compared the frequency of different symptoms in persons with putative MCS resulting from different exposures. In one study, the frequency of reported symptoms in MCS patients with self-reported pesticide exposure was compared to the frequency of reported symptoms in persons with MCS following building remodeling. Frequencies of symptoms resulting from a long list of inhalants and food were similar in the two groups, though severity of symptoms for all organ systems affected was higher for the pesticide group (see Figure 11.1) (Miller and Mitzel, 1995). Similarly, comparing four groups of MCS subjects (patients with sick-building syndrome, chlorine dioxide exposure, OP pesticide exposure, and exposure to individual organic solvents) resulted in health and illness status reports and specific organ system symptom reports that were similar within MCS groups and different between MCS groups and controls for 11 of 12 symptom categories (the twelfth was diagnosed autoimmune conditions) (Davidoff and Keyl, 1996). These similarities occurred despite the fact that the four groups had remarkably diverse demographics. Demonstration of similar symptom frequencies for these groups enhances validity of the MCS symptom complex. Evidence for a possible link between illnesses in PGW veterans and the MCS complex would be strengthened or weakened to the extent that rankings of symptoms reported by ill PGW veterans agreed or disagreed with symptom rankings in those with the presumed MCS symptom complex.

(Claims that stress or “psychogenic illness” is substantially responsible for illnesses in PGW veterans can and should be subjected to the same minimal scrutiny. That is, the fraction of ill subjects who have various symptoms following other stressful circumstances would be expected to be similar to the fractions with the same symptoms among PGW veterans for the stress hypothesis to be supported. To the extent this is untrue, the stress hypothesis is weakened. No attempt to verify quantitative comparability of symptom frequencies in illness following major stressors has been identified.)

As noted previously, Miller (1996b) reported quantitatively similar ordering of symptoms (using eight symptom scales derived by factor analysis) in 59 consecutive ill PGW veterans (of whom 78 percent reported new onset chemical sensitivities since the war) as in 37 pesticide-exposed civilians with chemical sensitivities, in non-peer reviewed testimony (Miller, 1996b). These results were quite different from those in normal controls. If ranking of symptoms referable to different organ systems are indeed confirmed to be similar in PGW veterans and MCS patients, this strengthens the case for operation of a similar mechanism for illnesses in some PGW veterans.



SOURCE: Miller (1996a)

Figure 11.1—Comparison of Symptom Severity

SUMMARY

The lack of a clinical case definition for either MCS or illness in PGW veterans complicates the examination of a connection. Therefore and predictably, any connection between MCS and illnesses in PGW veterans is based on weak and indirect evidence. One unpublished study finds a high rate of new chemical sensitivities in ill PGW veterans. The same investigator reports evidence of similar symptom frequencies for the two conditions (Miller, 1996a). These findings require confirmation and replication in peer-reviewed sources. One postulated mechanism for MCS involves cholinergic system activity, perhaps linked to limbic system kindling. PB with stress or chemical combinations might be expected to facilitate development of MCS if this mechanism is substantiated. Other postulated mechanisms for, or contributors to, MCS (such as nasopharyngeal mucosal dysfunction) could also be linked to cholinergic dysfunction. Evidence of brain SPECT abnormalities in PGW veterans with chemical sensitivities needs to be confirmed in a larger sample, with blinded reading of SPECT images. SPECT abnormalities have also been reported in subjects exposed to pesticides and may suggest that chemical exposures underlie symptoms in PGW veterans with chemical sensitivities. Whether similar SPECT

abnormalities will be seen in larger samples of ill PGW veterans with subjective chemical sensitivities, or in those without subjective chemical sensitivities, remains to be determined. EEG findings in MCS parallel those in pesticide-exposed individuals, providing some internal consistency for toxin-induced illness in MCS. Moreover, similar EEG abnormalities have been observed with exposure to other AChE inhibitors including sarin, which is an AChE inhibitor to which some PGW veterans may have been exposed. Therefore, careful EEG and SPECT studies may be warranted in ill PGW veterans with and without reported chemical sensitivities and in controls to evaluate whether chronic abnormalities in brain activity are present by this measure. However, a cogent interpretation of a positive finding may be complicated by the presence of EEG and SPECT abnormalities in some psychiatric conditions.

Although the connection between MCS and illnesses in PGW veterans is supported only by limited evidence, enough suggestive evidence is present to warrant further scientific study.

SCIENTIFIC RECOMMENDATIONS

Future work should concentrate on the following:

- Ascertain (replicate in a larger sample) the fraction of PGW veterans, ill PGW veterans, and controls reporting new chemical sensitivities.
- Ascertain (replicate in a larger sample) whether (rank-ordered) symptoms in ill PGW veterans (and/or in PGW veterans reporting chemical sensitivities) occur with similar rank and at frequencies consistent with those of patients with putative MCS.
- Ascertain whether ill PGW veterans with chemical sensitivities share similar EEG abnormalities with subjects exposed to pesticides and with MCS patients.
- Evaluate whether enzyme polymorphisms or low enzyme levels (e.g., paraoxon, BChE) partially discriminate OP-exposed subjects who develop MCS versus similarly OP-exposed subjects who do not and PGW veterans who develop illnesses and those who do not.
- Evaluate whether respiratory mucosal epithelial abnormalities (perhaps including measures of nasal resistance and of neutral endopeptidase) are present in ill PGW veterans with chemical sensitivities compared to controls and replicate the presence or absence of these abnormalities in MCS.
- Evaluate (replicate in a larger sample, using blinded qualitative readings supplemented by quantitative SPECT) whether SPECT abnormalities char-

acterize ill PGW veterans with and without chemical sensitivities, compared to matched controls.

- Evaluate whether quantitative SPECT shows differences in cerebral perfusion before exposure to a target chemical (after a period of “unmasking”) and after exposure, and whether these findings differ for those complaining of new sensitivities compared with those not complaining of such sensitivities and in ill PGW veterans compared with healthy controls, in an effort to develop an objective marker for chemical sensitivity and for illness in some PGW veterans.

SUMMARY ANALYSIS

Compatible Exposures

Many veterans are known to have been exposed to AChE-inhibiting chemicals (including PB, pesticides, and low-level nerve agents), which some feel may predispose to subjective chemical sensitivities.

Compatible Illness

Unpublished, non-peer reviewed research reports new chemical sensitivities in a high fraction (78 percent) of a small number (59) of tested ill veterans. Unpublished, non-peer reviewed research finds that ranking and frequency of symptoms is similar in these veterans and in non-PGW patients with subjective chemical sensitivities following self-reported exposures. No peer-reviewed evidence is yet available to support or refute these findings.

Compatible Link Between Exposure and Illness

No published effort has been made to link presence of “compatible” exposures to new subjective chemical sensitivities in PGW veterans.