Integrated Defense System Overlaps as a Disease Model: With Examples for Multiple Chemical Sensitivity

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The central nervous, immune, and endocrine systems communicate through multiple common messengers. Over evolutionary time, what may be termed integrated defense system(s) (IDS) have developed to coordinate these communications for specific contexts; these include the stress response, acute-phase response, nonspecific immune response, immune response to antigen, kindling, tolerance, time-dependent sensitization, neurogenic switching, and traumatic dissociation (TD). These IDSs are described and their overlap is examined. Three models of disease production are generated: damage, in which IDSs function incorrectly; inadequate/ inappropriate, in which IDS response is outstripped by a changing context; and evolving/learning, in which the IDS learned response to a context is deemed pathologic. Mechanisms of multiple chemical sensitivity (MCS) are developed from several IDS disease models. Model 1A is pesticide damage to the central nervous system, overlapping with body chemical burdens, TD, and chronic zinc deficiency; model 1B is benzene disruption of interleukin-1, overlapping with childhood developmental windows and hapten-antigenic spreading; and model 1C is autoimmunity to immunoglobulin-G (IgG), overlapping with spreading to other IgG-inducers, sudden spreading of inciters, and food-contaminating chemicals. Model 2A is chemical and stress overload, including comparison with the susceptibility/sensitization/triggering/spreading model; model 2B is genetic mercury allergy, overlapping with: heavy metals/zinc displacement and childhood/gestational mercury exposures; and model 3 is MCS as evolution and learning. Remarks are offered on current MCS research. Problems with clinical measurement are suggested on the basis of IDS models. Large-sample patient self-report epidemiology is described as an alternative or addition to clinical biomarker and animal testing. — *Environ Health Perspect* 106(Suppl 1):85–109 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/85-109rowat/abstract.html*

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Integrated Defense System Overlaps as a Disease Model

Nervous, Immune, and Endocrine Integrated Defense Systems

Over past decades researchers have identified several context-specific response systems that are combinations of the central nervous, immune, and endocrine systems and their messengers. In this paper these are termed integrated defense systems (IDSs).

The following IDS have been studied and reported in the literature: time-dependent sensitization (TDS), immune response to antigen (IRA), kindling, nonspecific immune response (NIR), acute-phase response (APR), stress response (SR), neurogenic switching (NS), tolerance, and traumatic dissociation (TD).

As Figure 1 illustrates neuroimmune–endocrine interactions of these IDSs are complex. There are homeostases within each of the central nervous, immune, and endocrine systems with multiple messengers running between them. Many of these messengers travel between two sets of the systems such as thymic peptides, adrenocorticotropic hormone (ACTH), tumor necrosis factor alpha (TNF-α), and interleukins, or between all three such as β-endorphins and interferons. This overlap indicates not only that any one IDS is likely to invoke wide systemic responses but also that overlaps and cross-interactions among the IDSs themselves are possible.

Overlaps and Interactions among Integrated Defense Systems

Many IDSs are involved regularly in defense response. In exploring possible significant interactions among them, the following points can be made.

* All IDSs have a range of known symptomatic response that extends across at least two of the nervous, endocrine, and immune systems, and several encompass all three. This is shown graphically in Figure 2.
* Many of the IDSs use identical messengers, cells, and tissues to accomplish their responses (interleukin-1 [IL-1], interferons, ACTH, endorphins, T cells, substance P, neurotransmitters, etc.) Some known overlaps are collated into Table 1. (Also see "Range of Physical Action" in the individual IDS descriptions in the following section.) Because we are still discovering messengers at an appreciable rate [for instance, substance P (1) and the range of effect of the interleukins (2)], actual overlaps may be greater than we know at present.
* Many IDSs have identical inciters (Table 1). For instance, eight of the nine IDSs are known to be incited by exogenous chemicals and six by microorganisms. There is either direct or partial evidence that all nine are induced by physical stress, seven by endogenous chemicals, seven by psychological stress, etc.
* Many of the IDSs have a long time-range [for instance, months or years with TDS (3), TD, tolerance, kindling (4), and aspects of IRA (5)]. Temporally overlapping activity of several is therefore possible. With multiple or chronic stressors, some temporal overlap becomes inevitable.
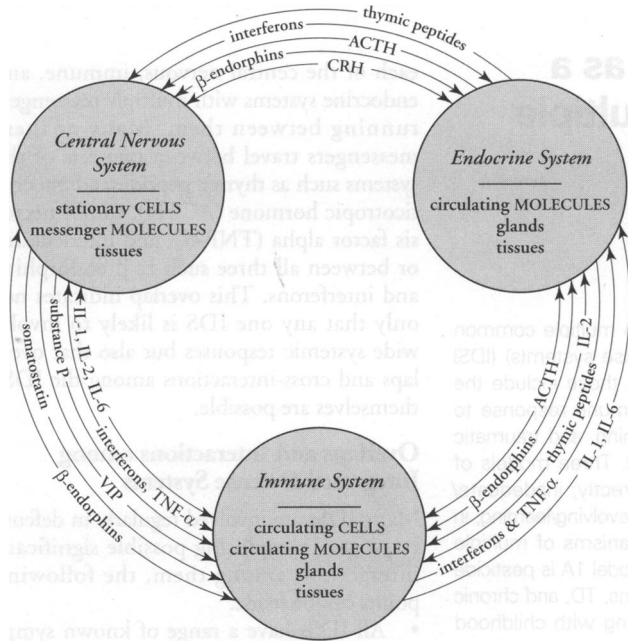* Many IDSs are reported to operate through a threshold mechanism [TDS

Figure 1. Messenger overlaps between the nervous, immune, and endocrine systems. Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; TNF, tumor necrosis factor; VIP, vasoactive intestinal peptide.
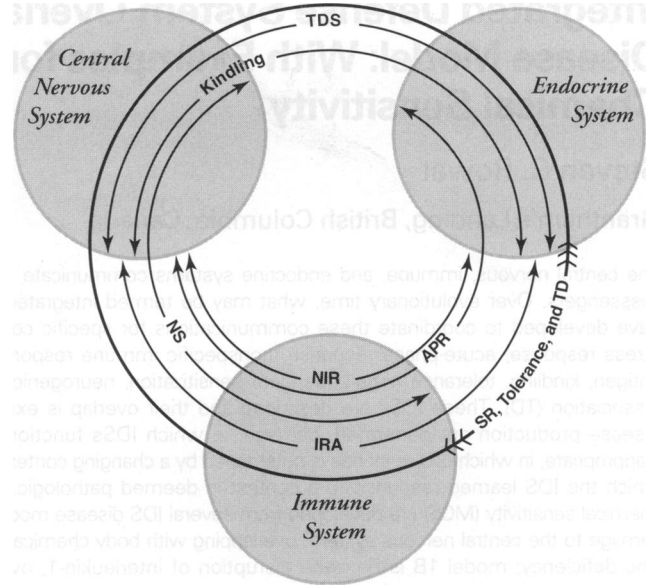

Figure 2. Overlaps in range of symptomatic response of nine IDSs across the nervous, immune, and endocrine systems.

Table 1. Reported range of physical action and inciters for IDSs.

Action and inciters	IDS								
	TDS	IRA	Kin	NIR	APR	SR	NS	Tol	TD
Range of physical action									
Limbic brain structures	●		●			●		●	●
Cortex and higher brain	●		●			●	○	●	●
Other brain structures	●					●		●	●
Peripheral CNS cells				○			●	●	○
Dopamine and norepinephrine	●		●			●		●	●
Serotonin and GABA	●		●			●		●	●
Substance P, VIP, somatostatin	●							○	○
ACTH	●					●		●	●
β-Endorphin	●	●				●		○	●
Prostaglandins	●					●		●	●
Other hormones	●					●		●	●
Zinc and MT	●	●	●	○		●		●	●
IL-1	○	●		●	●	●	●	●	●
IL-2	○	●		●	●	●		●	●
Other interleukins	○	●		●		●		●	●
TNF	○	●		●		●		●	●
T and B cells	○	●		●		●		●	●
Mast cells	○	●		●		●		●	●
Other immune cells	○	●		●		●		●	●
Histamine		●		●		●			●
IgA, IgG, IgE, IgM		●		●		●		●	●
Complement		●		●		●	○	○	○
Inciters									
Exogenous chemicals	●	●	●	●	●	●	●	●	●
Endogenous chemicals	●	○	●	●	●	○	●	○	
Psychological stress	●	●	●	○		●	●	○	●
Physical stress	●	●	●	○	○	●	●	○	○
Microorganisms		●		●	●	●	●	●	●
Foreign tissues		●		●		●		●	●
Self tissues		●		●		●		●	●
Metals		●		●		●		●	●
Foods		●		●		●		●	●

Abbreviations: Kin, kindling; Tol, tolerance. ●, Direct evidence of involvement. ○, Partial evidence of involvement.

(*3*), kindling (*4*), SR (*6*), IRA (*7*)] and conceivably all do. In some cases a threshold is even fired by other IDSs in a chain reaction; for instance, the NIR can lead to the APR, which can lead to the SR.

- Conditioning—associative learning—among the central nervous, immune, and endocrine systems has been documented and reviewed (*8–10*). For instance, selective immune parameters can be trained to change with central nervous system (CNS)–endocrine signals derived from taste (*11*), smell (*12*), audiovisual signals (*13*), and psychologic stress (*8,14–16*). CNS–endocrine emotions such as fear (*17*) can be conditioned to perceptions (sound, context), and CNS–endocrine symptoms such as anxiety, sleep disorders, irritability, and depression have been suggested to be classically conditioned responses to environmental odors (*18*).

The foregoing overlap data infer that there is strong potential for interactions between IDSs. For example Table 1 shows that there is direct or partial (d/p) evidence that psychological stress can incite seven of the nine IDS—TDS, IRA, NIR, SR, NS, tolerance, and TD. If we look at the ranges of physical action of these seven IDSs, we find that many are using the same messengers. For instance, all seven have d/p evidence of using IL-1, IL-2, T and B cells, and other immune cells; six have d/p evidence for using mast cells, TNF, other interleukins, Zn, and metallothionein; (MT); five have d/p evidence of using ACTH, β-endorphins, immunoglobulins, and proteins of the classic or alternative pathways of the complement cytolysis system; four have d/p evidence of using limbic brain, cortex, peripheral nerve cells, dopamine and norepinephrine, substance P, vasoactive intestinal peptide (VIP), somatostatin, and other hormones, and three have d/p evidence of using other brain structures, serotonin and γ-aminobutyric acid (GABA), prostaglandins, and histamine.

If this overlap data is combined with the points listed above—the IDSs similarities in their range of symptomatic responses, the use of thresholds by the IDSs (some of which chain), long timeframes of certain IDSs, and conditioned learning, which cross-fertilizes inciters and triggering cues—there is potential for confounded activity among the IDSs that may include long-term learning of new thresholds of response. Such activity conceivably includes some existing diseases and syndromes. It may be especially useful to consider problematic diseases and syndromes like fibromyalgia, chronic fatigue, and multiple chemical sensitivity (MCS), which defy conventional analysis and often are postulated to be multifactorial conditions. Example models are generated for MCS in "MCS Mechanisms Generated from IDS Overlap Models."

IDS Disease Production Model Types

To narrow the vast list of IDS interactions we are faced with in Table 1, it may be useful to examine types of IDS disease production. If we posit a rapidly changing environmental context—a human immersed in levels of chemicals and stress that are outstripping the evolutionary time required originally to build the IDSs—we might see these three types of new interactions:

- Damage to IDSs, in which one or more of the IDSs no longer functions correctly because of a physical distortion or loss of one of its parts and in which its/their interactions with the other IDSs are also crippled.
- Inadequate or inappropriate response from IDSs, in which a radically changing context includes new inciters or new concentrations of known inciters that induce pathologically inadequate responses from one or more IDSs.
- Evolving or learning IDSs, in which a changed context is mirrored by novel learning, including genetic learning, by one or more IDSs, giving rise to a new range of response.

When faced with a puzzling disease entity, we may then ask the following three questions about each IDS. Has the IDS been damaged? Has the context to which the IDS responds been changed so much that the IDS's range of response is no longer adequate? Has the IDS learned a new range of response to reflect a changed context?

Depending on the answers to these questions, we can build a combining hypothesis for the disease mechanism with several IDSs involved. This mechanism can include more than one type of IDS change. For instance (in a random example for illustration only): *a*) benzene can damage the immune response to antigen (*19*); *b*) continuous ambient air pollution such as NO_2 produces a tolerance response, but with rising levels tolerance is eventually inadequate and is exhausted (*20*) and is followed by pathologic tissue changes; *c*) a child raised in an environment of severe abuse and neglect and without any caring adult support frequently will evolve a coping pattern that includes changes in, among other things, SR to aggressive situations, involving catecholamine, cortisol, serotonin, and endogenous opioid response changes (*21*).

If all three of these IDS changes were to occur in one person specific repeatable symptoms would be observed based on the interaction between the damaged IRA, the exhausted tolerance to NO_2, and the modified (evolved) SR. If this specific constellation of IDS changes was to occur among a large number of people, reflecting a broad environmental context change in benzene concentration, NO_2 concentration, and frequency of child abuse, then the resulting similarity of symptoms across separate patient case histories could be called a syndrome.

In this paper it is suggested that working backward from case histories using the IDS framework can in some instances reveal which IDS interactions cause the syndrome.

Individual IDS Descriptions

In "MCS Mechanisms Generated from IDS Overlap Models" MCS mechanisms are modeled as malfunctions and interactions of the nine IDSs. To accomplish this an understanding of the individual characteristics of IDSs is useful. Definitions drawn from the scientific literature, as well as a range of physical action, are given for each IDS. It is assumed that most readers will be familiar with most but not all the IDSs; therefore, more detail for each IDS, including a description of mode of action and inciters, is confined to the Appendix. Range of physical action and inciters are summarized in Table 1.

The full description of TD is included at the end of the listing below rather than in the Appendix, and readers are encouraged to examine it. The recent research into severe psychological trauma, including severe child abuse, has shown that it frequently produces permanent biological changes, and severe child abuse recently has been convincingly linked to well-known adult psychiatric dysfunctions. This background may be useful in understanding how TD could be an appreciable factor in widespread IDS interactions. The nine IDSs considered, along with referenced definitions and ranges of physical action, are listed below.

Time-Dependent Sensitization. "TDS refers to the ability of mild stressors—whether pharmacological or environmental—to induce physiological and behavioral effects which then progress, i.e., get stronger, entirely as a function of the passage of time since stressor presentation" (*3*).

"TDS is the progressive and persistent amplification of behavioral, neurochemical, endocrine, and/or immunological responses to repeated intermittent stimuli over time" (22).

The range of physical action includes neurotransmitters such as dopamine, norepinephrine, serotonin, GABA, and aspartate (3); hormones (corticosterone, ACTH, β-endorphin); and immune system (3). Zinc is implicated in GABA (23–25) function.

Immune Response to Antigen. "The main feature that separates vertebrate from invertebrate immune systems is the ability to generate antigen-specific lymphoid cells" (26).

"[T]he immune system...learns to recognize foreign organisms and exhibits the property of memory. It remembers that it has seen a foreign organism and on its second encounter with that organism, it attacks more rapidly and more efficiently" (27).

The range of physical action for the IRA includes T- and B-cell receptors for specific antigens; thymus-directed T-cell growth processes including gene encoding for receptors (28); T- and B-cell multiplication; B-cell production of antigen-specific immunoglobulin antibody molecules including immunoglobulin (Ig)A, IgG, IgE, and IgM; T-cell production and reception of messengers including interleukins (IL-1 through IL-8). The range also includes TNF (2); platelet-activating factor (29); T- and B-cell production and reception of hormones including ACTH and β-endorphin (30,31); T- and B-cell receptors for CNS messengers such as substance P (1,32), VIP (32,33), and somatostatin (32), and for endocrine hormones such as thymulin (34). Zinc is required for thymulin activation. For a review of dozens of messengers between the nervous and immune systems, see Plata-Salaman (29).

Kindling. "[K]indling refers to neural processes that mediate lasting changes in brain function in response to repeated, temporally spaced application of neurobehaviorally active agents" (35).

"Partial limbic kindling is a progressive and persistent lowering of the threshold for eliciting electrical after-discharges, but not motor seizures, in certain brain structures such as amygdala and hippocampus; behavioral consequences include increased avoidant behaviors" (22).

The range of physical action for kindling includes various brain structures, e.g., the cortex (36) and especially the limbic brain including the olfactory bulb and amygdala

(37). Changes in brain chemistry are found, including a decrease in acetylcholinesterase enzyme activity that parallels the increase in sensitivity (37). Calcium-binding protein and tyrosine hydroxylase activity are reportedly reduced, and there are changes in β-noradrenergic binding (36). Benzodiazepine receptor binding is modified (36), as are transmitter GABA and N-methyl-D-aspartate functions (4). Zinc may be implicated through GABA (23–25). Superoxide dismutase may also be involved (38). "These changes may be irreversible" (37).

Nonspecific Immune Response. "Long before the appearance of antigen-specific T cells or antibodies, the body is able to deploy an impressive array of humoral factors as a highly effective first line of defense against potential pathogens" (39).

The range of physical action for NIR includes circulating mast, natural killer (NK), macrophage, B, and T cells and their produced molecules such as TNF-α, IL-1 through IL-6, granulocyte-macrophage colony-stimulating factor (GM–CSF) (40) and histamine (1). Other actions include collectins such as mannan binding protein (MBP), surfactant protein-A, and surfactant protein-D (39); and complement components such as C1r, C1s, C4, and C2 (39) which are serum proteins that respond to antigen–antibody complexes (primarily) by generating an enzyme cascade that effects the membrane attack complex for cytolysis.

Acute-phase Response. "In the aftermath of injury, trauma or infection of a tissue, a complex series of reactions are executed by the host in an effort to prevent ongoing tissue damage, isolate and destroy the infective organism and activate the repair processes that are necessary to return the organism to normal function" (41).

The range of physical action for APR includes circulating cells such as macrophages, monocytes, platelets, and mast cells; stromal and endothelial cells local to damage; cytokines such as IL-1, TNF, IL-6, and possibly IL-4 and IL-8; thromboxane A2, and prostaglandins I2, E2, D2, and F2α. Also included are leukotrienes B4, C4, D4, and E4, bradykinin; ACTH; glucocorticoids including cortisol; β-endorphin; Zn; MT; and many liver-mediated proteins such as glycoprotein, C-reactive protein, complement C3, fibrinogen, and antiproteases.

Stress Response. "Stressors are the disturbing forces or threats to homeostasis, and adaptive responses include physical or mental reactions that attempt to

counteract the effects of the stressors or disturbing forces in order to re-establish homeostasis" (6).

The range of physical action for SR includes brain regions: hypothalamus, brain stem, limbic system, and cortex; pituitary gland, adrenal gland, corticotropin-releasing hormone (CRH), ACTH, β-endorphins, glucocorticoids, adrenergic system, and catecholamines. It also includes immune cells (macrophages, T, B, and NK cells); cytokines IL-1, IL-2, IL-3, IL-6, TNF, prostaglandins including PGE2; adenosine monophosphate (42); tissue Zn (43,44), and brain Zn (45).

Neurogenic Switching. "Neurogenic switching is proposed to result when a sensory impulse from a site of activation is rerouted via the central nervous system to a distant location to produce neurogenic inflammation at the second location" (46).

The range of physical action for NS includes immune system mast, T, B, and other cells; CNS peripheral cells; cytokines such as IL-1 and IL-2 communicating with both CNS and immune cells; neuropeptides such as substance P, somatostatin, and VIP communicating with both CNS and immune cells. Various regions of the central CNS may be involved in processing information during switching. Immune memory (cells and genetic coding) may also be involved in encoding the switching (10).

Tolerance. "Adaptation and tolerance are defined ultimately in biochemical and biological adjustments that enable organisms to survive...[T]olerance is characterized, not only by repair, but also by the development of refractoriness or immunity to the persistent insult so that repair at the [same] level is no longer required in the usual sense..." (20).

"Symptoms of exposure to many chemicals, whether inhaled or ingested, appear to follow a biphasic pattern. Adaptation is characterized by acclimatization (habituation, tolerance) with repeated exposures that result in a masking of symptoms" (47).

"The stage of resistance represents the sum of all nonspecific systemic reactions elicited by prolonged exposure to stimuli to which the organism has acquired adaptation as a result of continuous exposure. It is characterized by an increased resistance to the particular agent to which the body is exposed and a decreased resistance to other types of stress" (48).

"Oral tolerance is a term used to indicate antigen-specific systemic hyporesponsiveness after prior enteral (oral) exposure to that antigen" (49).

The range of physical action for tolerance includes multiple tolerance instances, mechanisms, and symptoms involving multiple organ systems (7,20,47–55); the entire nervous, immune, and endocrine systems are potentially involved.

Traumatic Dissociation. "Dissociation is defined in DSM-III-R [*Diagnostic and Statistical Manual, 3rd Ed., Revised*] as a disturbance or alteration in the normally integrative functions of identity, memory, or consciousness....a more precise definition of dissociation is required..." (56).

"Dissociation is one of the principal mechanisms by which people cope with overwhelming experiences. Dissociation terminates states of extreme physical and emotional arousal during the trauma, but over time dissociative processes may be activated by minor stresses and simple reminders of earlier trauma" (21).

"Dissociative states, used defensively at the time of abuse, may become a generalized defense in any situation where strong affect is aroused" (57).

"Dissociation may belong to the realm of biological mechanisms that are triggered by overwhelming trauma-related affects and events...." (58).

Current research and reviews assert that mild dissociation experiences are common in the general population (56) and that strong dissociation is a key and possibly defining component of post-traumatic stress disorder (PTSD) (21,59–62), borderline personality disorder (BPD) (57,58,60), and multiple personality disorder (MPD) cases (63). All these clinical psychopathologies are associated principally with childhood abuse (21,57–60,63–66) and their differences may represent stages and facets of the same underlying process (61,62,67,68).

Since the etiologies of PTSD, BPD, and MPD are only now being revealed and because they appear to overlap significantly (all three commonly involve child sexual abuse), TD as introduced here is modeled after dissociation as used by van der Kolk and Fisler (21,61,69) and others in which it refers to a combined biological–psychological mechanism central to all cases of PTSD, BPD, and MPD, and which also occurs in less extreme forms in nonpathologic populations.

TD, then, is an emergency defense system invoked during overwhelming inescapable psychological trauma, and modulates both cerebral logical organization and physiological affect regulation. Especially after chronic trauma in childhood, TD produces lasting changes in both, although the symptoms may not appear simultaneously.

MODE OF ACTION. Recent articles in attachment theory (59,70), a research and theoretical framework in developmental psychology, describe the building of a conceptual model of relationships in the infant mind as early as the end of the first year of life (70). Attachment researchers have identified several types of children with incomplete or deviant attachment behavior (called avoidant, resistant, and disorganized behavior). They have found these types of children to be the result of insensitive, inconsistent, and abusive parenting, respectively (59,70). These children are postulated to have developed incomplete or damaged internal models of themselves and their relationships to the outside world (70), possibly permanently, because abused children are known to more frequently become abusing parents (70).

Working from a framework of adult PTSD and BPD, van der Kolk and Fisler (21) postulated disrupted attachment (including that resulting from abuse) results in a biochemically based loss of conceptual control. Current perceptions that appear superficially similar to past trauma cause emotion-based fight or flight responses to occur immediately, without the mediation of an abstract internal model that could decide whether such responses are valid. van der Kolk and Fisler further maintain that "forty years of research on nonhuman primates have firmly established that...disruptions of attachment early in the life cycle (as occurs in child abuse) have long-term effects on the neurochemical response to subsequent stress, including the magnitude of the catecholamine response and the duration and extent of the cortisol response. There are also long-term effects on a number of other biological systems, such as the serotonin and endogenous opioid system" (21).

In humans as well, PTSD, BPD, and MPD have been associated with lasting biologic changes in either baseline levels or during response to stress. For PTSD measured in war veterans, this includes norepinephrine, cortisol, ACTH response to CRH, serotonin (71), endogenous opioids, lymphocyte glucocorticoid receptors (21,69), and regional brain-flow patterns (72). A serotonin function review has cited its low levels in BPD and shown low levels of serotonin to be related to hyperirritability, hyperexcitability, and hypersensitivity, pain sensitivity, and lack of an inhibitory response in behavioral systems subserved by the hippocampal/amygdala system, including conceptual processing of reward, punishment, and uncertainty (73).

MPD was only recently recognized as an intentionally secret condition and not as rare as had been thought (perhaps not rare at all). MPD may be a superordinate diagnosis that may contain any of the symptoms of PTSD, BPD, and other personality disorders (63). In MPD separate personalities may have different (allergic) immune reactions (65) as well as differing responses to the same substance (alcohol, foods, and medications) (65), different body temperature, heart rate, and skin temperature (66), different eye muscle malfunctions (visual acuity problems) (66) and insulin levels (74), different handednesses (65), and different brain wave patterns (66). Thus in extreme cases of TD (i.e., MPD), not only is there an altered response to stress, there is an altered psychologic and physiologic response to almost everything. The number of varying personalities, which can approach 200 (74), has been significantly connected ($p < 0.0001$) to the number of types of childhood trauma reported in a patient's history (65).

Thus overwhelming trauma, particularly in inescapable (61,75) or double-bind situations [such as abuse by father or other primary caregiver (76)], appears to make a conceptual shift or dissociation in how both the psychologic and physiologic systems respond to stress. When the trauma occurs during the formation of a child's conceptual models, especially chronically, the shift is likely to be much more intense.

RANGE OF PHYSICAL ACTION. TD physical actions vary with the degree of dissociation; pathologically in PTSD and BPD they include many, and perhaps all, brain, endocrine, and immune systems that are involved in the SR such as cortisol, CRH, ACTH, norepinephrine, and lymphocytes; serotonin and possibly GABA and other parts of the noradrenergic system; and endogenous opioids. Although less well understood, TD also affects whatever higher-level brain centers subserve amnesia for self and place and for depersonalization and derealization experiences [such as not recognizing one's reflection in a mirror or looking at the world through a fog (56)]. In MPD the range of physical action includes all the foregoing plus whatever brain, immune, and endocrine areas and mediators are required to differentiate insulin levels, heart rate, skin temperature, allergic reactions, responses to foods and medications, eye acuity, handedness, and

brain wave patterns. In other words, most if not all body systems are included.

INCITERS. TD inciters are primarily conceptual: inescapably traumatic (frightening) events; i.e., child physical and particularly sexual abuse, war, rape, torture, domestic violence (72), and natural disaster experiences (69).

MCS Mechanisms Generated from IDS Overlap Models

Multiple Chemical Sensitivity: A Working Definition

A population of patients has emerged that reports elevated responses to low levels of environmental chemicals and adverse reactions to foods. One working group has termed these patients people reporting chemical sensitivity (77). They appear to come from four population categories that have been well-characterized elsewhere (78). These categories are: industrial workers, workers in tight buildings, people in contaminated communities, and individuals with and without acute chemical exposure histories.

Deciding who has MCS is problematic; the recently begun search for MCS biomarkers so far has been inconclusive (79–82). However, in the literature and based on extensive clinical experience, working definitions have evolved; this paper will use one similar to that proposed by Miller (83) and Miller et al. (84), with one notable difference: inclusion of the stress context.

Miller (83) proposes that MCS can be confirmed when, in a clean environmental medical unit (EMU), the following conditions are true: a) when a subject simultaneously avoids all chemical, food, and drug incitants, remission of symptoms occurs (unmasking); b) a specific constellation of symptoms occurs with reintroduction of a particular incitant; c) symptoms resolve when the incitant is again avoided; and d) with reexposure to the same incitant, the same constellation of symptoms reoccurs, provided the challenge is conducted within an appropriate window of time.

Working within the IDS overlap framework provided in "Integrated Defense System Overlaps as a Disease Model," a problem with this definition is that a particular form of psychological stress may be integral to the combined IDS response. For example, if TD has modified the SR and thereby modified the thresholds of other IDSs that use the same messengers (as modeled in the examples that follow), the

above definition could lead to the improper attribution of symptoms to MCS if a concurrent psychological triggering of the SR is necessary for the low-level chemical response to occur. Because it is probable such a stress is not provided by the EMU, no response is found and MCS is therefore invalidated as a causative factor. Yet the response occurs again when the patient is in his or her normal (psychologically stressed) environment. Conversely, the patient may find the EMU stressful to the degree that it is not possible to unmask the symptoms. Consider the following report of a 21-year old patient with PTSD (whose response to chemicals is not reported): "A lot of times I wake up at two, three o'clock in the morning and I'm having an anxiety attack before my eyes even get open. Sometimes it's that I'm dreaming, because that [clinic visit] is still going around in my head, even though it was six months ago. I'm really scared of this one doctor, and a lot of times he's in [the dream]...I hyperventilate, and I can't breathe, and I have stomach spasms, muscle spasms, and sometimes I throw up after it's over" (85).

Bell et al. (86) expressed similar concern for MCS testing protocols because animal work shows TDS sensitization in one environment does not replicate in a novel environment. To put it simply: context matters.

Thus it may be that in searching for an MCS definition and mechanism the attempt to isolate the patient from the context is premature; patients' reports of what is happening to them in their own words may be our best source of data for formulating hypotheses of what is occurring. At present the only widely available forms of these reports are a few extremely moving self-reports that have appeared in the scientific literature (87,88) or the popular press and, importantly, collated data from clinicians (89–93), including attempts by clinicians to define the condition [collated by Miller (90)].

This wealth of rich, awkward, and unfinished data and other published reports, along with my own experiences with people reporting chemical sensitivity, have been used to generate the IDS-overlap MCS models to follow.

IDS Overlap MCS Examples: Introduction and Summary

What appears to be required in the study of MCS—with its variable biomarkers, multiorgan symptoms, and diverse patient demographics—is a model that allows variable

biomarkers and symptoms among different hosts, and even in the same host at different times. For instance, a review of immunologic data reported on MCS (94) notes many abnormalities; some of these, however, are in opposite directions: T-cell helper/suppressor ratios reduced in several studies but raised in another; unusual amounts of autoantibodies in some studies but not in others; reductions in absolute T-cell counts in some studies and increases in others. Elsewhere a study of immune marker alterations among several hundred workers at a computer factory exposed to various chemicals showed a split skew with significant increases or decreases in T-cell helper/suppressor ratios as well as autoimmune markers (95). Work with single-photon emission-computed tomography brain scanning of veterans with chemical sensitivities (96) shows differences during the triggering state; this suggests a coded response but there does not appear to be traceable damage to any system. The task then may not be to find a linear marker for MCS, but to understand and extract from the data more complex changes in mechanisms underlying the biomarkers.

The overlap and chaining of thresholds in the examples developed below are suggested as first attempts at models that include nonlinear interactions between linked homeostatic systems. Mathematically they probably would best be expressed by a set of linked differential equations, although the explicit mathematics are not presented here. [Mathematics might best be supplied by chaos theory, which has been used to develop a model of the immune system as a dynamic adaptation system (27,55) to model the coevolution of hosts and parasites (97,98) and to study pathology (99), psychology (100), physiology (101), and a large number of other biomedical disciplines (102–107)].

Examples of the following MCS models produced through IDS interaction will be considered in the balance of this paper. Some are included because parts of their mechanism have been directly suggested by the MCS clinical literature; others are included because they are known to be widespread phenomena and their IDS interactions appear capable of generating MCS symptoms.

Six models are considered separately; they are grouped as follows:
1. MCS attributable to damage of IDSs
   1A. Pesticide damage to the CNS
   1B. Benzene disruption of IL-1 maturation

1C. Autoimmunity to IgG or vinyl chloride disease
2. MCS attributable to inadequate or inappropriate response from IDSs
   2A. Chemical and stress overload (using a combination of formaldehyde, air pollutants, anxiety, benzene, alkylphenol novolac resin, and anger)
   2B. Mercury allergy in a genetic subset (to increased levels of mercury in dental applications, food, and paint)
3. MCS attributable to evolving or learning IDSs
   3. MCS as evolution (a semantic exploration)

IDS Overlap MCS Model 1A: Pesticide Damage to the CNS

Introduction. Pesticides, including chlorpyrifos, are widely implicated in case histories and clinical reports of MCS (*89,91, 108–112*), both in terms of outbreaks of MCS after group exposures and of patient attributes of exposures that precipitated their condition.

Certain widely used pesticides that have disrupting effects on GABA neurotransmitters (*4,75,113*) may be initiators of kindling (*4*). This interference may also extend to polychlorinated biphenyls (PCBs) (*75*) and in general to organophosphate (OP) and organochlorine compounds (*113*). Some organochlorine insecticides such as chlorpyrifos reportedly cause both chronic neurologic symptoms (*114*) and modulation of the IRA (*112*). Certain OP insecticides enhance the large-fiber distal axonopathy caused by other OPs such as chlorpyrifos (*109,114*). Recently reported studies of Gulf War veterans confirm earlier reports of a connection between a syndrome of neurologic damage and wartime exposure to pesticides and insecticides (*115–118*).

Initial Damage. If we assume a relatively severe exposure to an OP such as chlorpyrifos with a coexposure to a synergistic damage-promoting solvent or other OP, there can be initial disruption of the GABA neurotransmission as well as damage to long nerve cells. It is also fair to assume that the nerve damage initially will invoke the NIR and, if the damage is sufficient, the APR.

Examining the IDS overlaps in Table 1, we see that the disruption of GABA may cause kindling and TDS to malfunction, as both use GABA. We also see that a large number of other messengers have been invoked by the NIR and the APR, including ILs, immune cells, ACTH, and

β-endorphin. ACTH and β-endorphin, however, are also used by TDS. Because we are assuming that the GABA disruption also changed TDS, the situation is unstable. In one direction TDS may modify the APR through ACTH and β-endorphin; in the other direction the APR may change TDS further, possibly including changing its threshold of reaction to incitants or the magnitude of its response. This bidirectional interaction is shown in Figure 3.

Extensions. With reference to Table 1, several major complications can be envisioned that would increase the chances of IDS interaction in this model; three will be discussed briefly.

BODY BURDENS AND SYNERGIES OF TOXIC CHEMICALS, INCLUDING PESTICIDES. Various chemical contaminants such as dioxins, PCBs, insecticides, and pesticides are reported in human tissue at levels that arouse concern (*119–125*). Because several chemicals are known to be present simultaneously

in the normal body burden (*119,125*), synergies may occur. Examples are carbon tetrachloride with chlordecone (*126–128*) and chlorpyrifos with other OP pesticides (*109,114*). This could mean continuous disruption of GABA and unstable action of ACTH and β-endorphin, possibly leading to unanticipated threshold changes in the TDS of various chemicals.

PREEXISTING TD. If a patient has a history of trauma sufficient to have modified his or her SR, psychological cues may incite changes in many messengers that also affect TDS, including dopamine and norepinephrine, ACTH, β-endorphins, Zn, IL-1, and other interleukins, hormones, and cells. Such stress occurring concurrent with new chemical exposure could be the mechanism by which the response is spread (as explored in model 2A). At least one study has reported higher rates of self-reported childhood abuse among women reporting MCS than among controls (*129*), and it may be
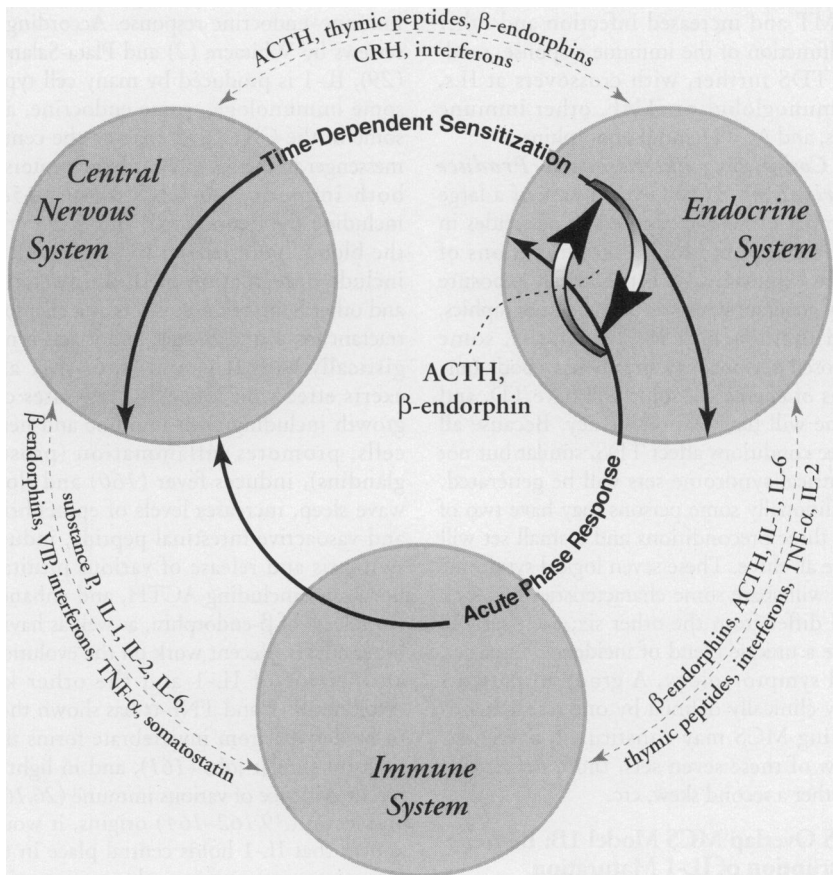

Figure 3. Modifications through overlap of messengers among IDSs. In multiple chemical sensitivity model 1A (pesticide damage to the CNS), TDS and APR are overlapping messengers ACTH, β-endorphin, various hormones, metallothionein, zinc, and possibly others (Table 1). Such overlap provides opportunities for both intended and unintended bidirectional influences, including modification of triggering thresholds and changing the functions of messengers unique to each.

more than chance that a significantly higher proportion of females than males report MCS, as a similar female:male ratio occurs among those who are estimated to be sexually abused in childhood; about 4:1 in the former (*130,131*) and 3:1 in the latter (*57*).

EARLY AND ONGOING ZINC DEFICIENCY. Zinc deficiency has been widely investigated in the last two decades and is now recognized to be a public health problem (*132*); a recent estimate is that 30% of the adult U.S. population is at risk. Zinc is centrally involved in multiple human systems (*133*), including GABA and other neurotransmitter enabling (*24,45,134–137*), and in sequestering and defense against heavy metals and chemicals (*138*). Gestational Zn deficiency appears to damage hippocampal and other functions (*44,45,139,140*). Chronic Zn deficiency reduces the IRA by deactivation of thymulin (*133,141–144*). Thus several crossovers with TDS are possible. Limbic structures and GABA may be malfunctioning because of early Zn deficiency; or ongoing chronic Zn deficiency may, through lack of MT and increased infection and other malfunction of the immune response, modify TDS further, with crossovers at ILs, immunoglobulins, TNF, other immune cells, and ACTH and β-endorphins.

Combining Extensions to Produce Variants of MCS.

Given a base of a large number of people exposed to pesticides in our society, the logical combinations of these extensions with the initial exposure may generate symptomology, demographics, and incidence of MCS. That is, some exposed persons may already have body burdens of chemicals, some will have TD, and some will have Zn deficiency. Because all three conditions affect TDS, similar but not identical syndrome sets will be generated. Additionally some persons may have two of the three preconditions and a small set will have all three. These seven logical syndrome sets will share some characteristics but each will differ from the other six; each set will have a unique blend of incidence, intensity, and symptomology. A group of patients now clinically defined by one researcher as having MCS may constitute a particular skew of these seven sets, those defined by another a second skew, etc.

IDS Overlap MCS Model 1B: Benzene Disruption of IL-1 Maturation

Introduction. In a series of recent experiments on mice and human *in vitro* cells, benzene through its metabolites has been shown to prevent bone marrow cells from producing mature IL-1, and this is thought

to play a central role in benzene-produced aplastic anemia (*19,145–148*). Combined with the immense amount of data on a large number of cancers and toxicities that benzene is known to cause (*149–157*) as well as its ubiquitousness in our environment, this makes it clear that we need to know more about its effect on IL-1 and possibly other cytokines, both in the bone marrow and in other body milieus. For instance various researchers have implicated benzene in human bronchial, colon, and liver damage, leukemia, DNA damage, tumors including brain, liver, stomach, and lung, cardiac abnormalities, eye irritation, drowsiness, unconsciousness, uncoordination, and heart attack (and in mice, birth defects and tumors). Benzene is present in gasoline (from auto exhaust, vehicle interiors, and gas stations), diesel exhaust, building materials, plastics, polypropylene food containers, cooked foods, printers, printed and copied paper, copy machines, incinerators, and tobacco, wood, and marijuana smoke.

IL-1 holds a central place in neuro-immune–endocrine response. According to reviews by Whitacre (*2*) and Plata-Salaman (*29*), IL-1 is produced by many cell types, some immunologic, some endocrine, and some in the CNS. IL-1 may be the central messenger in the SR (*29*), it has receptors in both immune and CNS tissue (*158*), including the brain (*158*), and it can cross the blood–brain barrier (*159*). Its effects include upregulation of IL-2, interferon, and other lymphokines; it acts as a chemoattractant for T and B cells, and it acts synergistically with IL-4 and IL-6. IL-1 also exerts effects on NK cells, regulates cell growth including both immune and nerve cells, promotes inflammation (prostaglandins), induces fever (*160*) and slow-wave sleep, increases levels of epinephrine and vasoactive intestinal peptide, induces synthesis and release of various pituitary hormones including ACTH, and enhances the release of β-endorphin, as well as having other effects. Recent work on the evolutionary origins of IL-1 and the other key cytokines IL-2 and TNF-α has shown them to be derived from invertebrate forms that perform similar jobs (*161*), and in light of recent evidence of various immune (*26,161*) and lectin (*39,162–164*) origins, it would appear that IL-1 holds central place in the first memory system, the nonspecific immune system, which predates even the existence of a CNS, much less a brain.

Along with the relatively new data about IL-1 suppression by benzene metabolites (*19,145–148*), benzene

metabolites induce leukemia and other DNA damage (*165–167*). If this damage occurs at levels sufficient to invoke any of the eight IDSs besides kindling, IL-1 is likely to be involved as part of the IDS response; IL-1 is the single most shared messenger among the body's IDSs (Table 1).

One MCS study has shown IL-1 to be produced in significantly reduced amounts from peripheral blood mononuclear cells in cases relative to controls (*81*), although the authors state that this may have occurred because of laboratory methodology problems. Notwithstanding the slightness of this evidence, the IL-1–benzene connection appears to be a reasonable candidate for MCS investigation if the suppression of IL-1 maturation in bone marrow by benzene metabolites also holds in the large number of other sites where identical IL-1 is produced. It also may be noteworthy that the list of benzene-containing substances is close to being a list of the MCS substances most highly reacted to. If we suspect that which chemicals MCS sufferers react to may be a meaningful guide to what caused the condition, benzene is a good place at which to start investigating.

Initial Damage. If benzene metabolites have also downregulated the IL-1 an IDS is using for its messaging, the IDS response to benzene may be changed. For instance if we assume that benzene exposure induces the APR, then because of the benzene downregulation of IL-1, other messengers in the APR could have distorted values; these include ACTH, β-endorphin, prostaglandins, other interleukins, mast cells, and other immune cells. TDS also uses ACTH and β-endorphin; if it is invoked, its threshold of response may be modified. If the benzene exposure has been sufficient to induce the SR, then the distorted IL-1 values may additionally affect TDS through limbic brain structures and dopamine and norepinephrine, and kindling through these and through cortex and higher brain structures.

Extensions. CHILDHOOD WINDOW EXPOSURES. Childhood exposure data indicate that if exposure to benzene (or benzene-derived chemicals that have similar metabolites) occurred during developmental windows, special damage or immune learning could occur. Gestational windows correlate a wide variety of fetal malformations, toxicities, and subsequent developmental problems with various pregnancy exposures to PCBs (*168*), antibiotics (*169,170*), anesthetics (*171–173*), and environmental chemicals (*174–177*). Infant developmental windows have been reported

to correlate hexachlorophene washing with neonatal brain damage and death (*178,179*). Such exposures of benzenoid chemicals may induce a TDS to benzene or its derivatives or an IRA to a hapten formed from such a chemical or its metabolites.

HAPTEN SPREADING FROM CONTINUOUS EXPOSURE. Antigenic haptens are formed from both aromatic and nonaromatic chemicals (*180–184*). An interesting series of experiments with acetaldehyde (*183,185–189*) has shown that the immune response successfully "...could be raised by immunizing with acetaldehyde conjugated to a carrier protein different from the one that is used for testing" (*185*). In other words the immune response could recognize the antigenic chemical segment and spread the reactivity to other carriers. In the case of acetaldehyde, usually IgE, and in one case IgG and IgM, is raised to acetaldehyde–protein adducts (*183*), and this has been used both in diagnosing alcoholism (*186,187*) and as an explanation for alcohol allergy (*183*). Benzene is the building block of the enormous number of new antibiotics, fuels, plastics, printing materials, food additives, pesticides, cleaners, and cosmetics that have been added to our environment in recent decades. If this immune recognition could happen with benzene metabolites or derivatives, the crossover between the IRA and another IDS, especially in light of the dysregulation of IL-1 by benzene, might account for both threshold response change and spreading found in MCS patients.

EARLY AND ONGOING ZINC DEFICIENCY. IL-1 and Zn–thymulin are synergistic. [Thymulin is central in T cell and other immune regulation (*34*) and Zn is required for thymulin function (*142,190*)]. IL-1 delivers Zn to thymulin via MT mRNA and Zn–thymulin potentiates IL-1 activation of nuclear protein kinase C in isolated splenocytes (*191*). Also, Zn deficiency in gestational and childhood windows, especially in conjunction with benzenoid environmental chemicals (*192*), reportedly causes a variety of malformations (*44,193*) including CNS development. Lack of Zn during early rat brain growth produces neurologic abnormalities (*44,139,140*). See additional discussion in section on model 1A.

BODY BURDENS OF TOXIC CHEMICALS INCLUDING PESTICIDES. Almost all the chemicals commonly in the body burden are benzenoid. See detailed description in section on model 1A.

PREEXISTING TD. In a human case–control study, psychological stress reduces the amount of IL-1 produced by peripheral blood leukocytes, which was correlated with the slowing of wound healing (*194*). See detailed description in section on model 1A.

Combining Extensions to Produce Variants of MCS. As discussed in the section on model 1A, these different situations can be combined to produce overlapping syndromes that could be subsets of MCS. Early window effects, hapten spreading, body burdens of benzenoid chemicals (and continuous exposure to benzene itself), preexisting TD, and Zn deficiency in early windows or later could interact individually with an IL-1 dysregulation model to increase or modify the effect. Any combination of two, three, four, or five of the extensions with the original could produce a different subset of symptoms and hence possibly appear as a different subset of the main syndrome.

IDS Overlap MCS Model 1C: (Vinyl Chloride Disease) Autoimmunity to IgG

Introduction. A fascinating variant of "Hapten Spreading from Continuous Exposure" is that it appears that immune system messengers themselves can become objects of immune response. This has been hypothesized as the central event in vinyl chloride disease (*95,195–197*), which may be a rheumatoidlike (*198*) autoimmunity to IgG after chronic vinyl chloride exposure damages the IgG molecule. Other chemicals that induce autoimmune disturbances include halothane (*184*) and acetaldehyde (*183*), and biomarkers and symptoms in such disturbances exhibit variable data in multiple organs (*197*), indicating that several effects on the IRA may be occurring. In addition, food lectins such as BanLec 1 (found in bananas) can be inciters of IgG; lectins also interfere with the complement NIR (*162,199,200*), commonly act as superantigens (*54,162*), and are endocytosed in relatively large quantities in the gut (*200*).

Initial Damage. In our model we assume that chronic exposure to vinyl chloride has damaged both IgG and other tissues and the IRA produces T-cell-mediated autoimmune complexes raised against these tissues (*196*). We do not know with certainty the memory mechanism of such autoimmune disturbances; possibly it involves DNA encoding in the variable (diversity) joining recombination of T cells (*26,28,201,202*). In addition T memory cells exist for long periods, decades at least, without any booster from antigens (*5,203*).

Extensions. SPREADING TO OTHER IgG-INDUCING ANTIGENS. Certain foods such as bananas, milk, and eggs produce unusually high levels of IgG allergic responses in pooled human blood (*199*). Soy (*204*), beef (*205*), and corn (*206*) also induce IgG, as do various chemicals (*181,182,206*). Suppose a subject consumes one of these substances and has an IgG reaction to it; by increasing the IgG level, the subject is simultaneously increasing the total autoimmune reaction to IgG itself. This may induce an additional IDS such as NIR to become involved.

Because the NIR is also known to induce the immunoglobulins, it becomes possible that a feedback loop will be set up: with more IgG comes more IRA and more NIR; with more NIR comes more IgG. This escalation could be sudden in certain conditions (like a painful audio feedback), and, by multiple crossover messengers, might induce the SR and TDS to the initiating foods or chemicals. In this way, a large number of IgG-provoking substances eventually could become inciters of a TDS response.

SUDDEN SPREADING—MULTIPLE IDS SENSITIZATION TO IgG. This possibility, though apparently supported by no direct experimental evidence, produces such an interesting model that it must be at least mentioned briefly. What happens if after IgG becomes antigenic and IgG-inducing substances are introduced, a feedback loop causes TDS both to the inciting substance and to IgG? A spreading/multiplier effect is then set up. Any inciter of IgG automatically becomes an inciter also of TDS, even without a specific spreading event. The subject would suddenly become sensitized to all the foods and chemicals that already incite IgG, such as those mentioned in "Spreading to Other IgG-inducing Antigens." This type of quick spreading matches an important and puzzling aspect of the MCS syndrome.

FOOD-CONTAMINATING CHEMICALS. The presence of pesticide residues, additives, and packaging migrants in commercial foods provides an opportunity for chronic or acute conditioned association between a chemical and an IgG-inciting food. Additionally, if such a chemical became complexed with the food before or during metabolism, the association would be different and possibly more antigenic. It is perhaps noteworthy that such complexing does not appear to have been studied; the literature on food contaminants (surprisingly sparse) deals largely with a few identified migrants and contaminants (*207–216*) rather than with their ability to complex with foods. The intense European

Economic Community initiative to develop measurement and reporting techniques for packaging migrants is based on specific lists of chemicals (217,218); unfortunately complexing with foods is not included.

Combining Extensions to Produce Variants of MCS. Reports of autoimmune markers in MCS patients (like most MCS data) are inconsistent. A recent report (89) shows antismooth muscle antibodies in about half the patients seen in a clinical practice but no data about anti-IgG antibodies or antibodies against any other IDS messenger. Although many MCS patients report food sensitivities, this model has been presented chiefly as illustration. It is plausible that any IDS messenger that could act as an antigen could provide a feedback mechanism for spreading of the MCS response. An MCS so produced could be viewed as a form of chemically formed autoimmune disease.

IDS Overlap MCS Model 2A: Chemical and Stress Overload

Introduction. In past decades the amounts and types of chemicals encountered indoors and outdoors in food and air have risen exponentially (78). Workplace environments contain chemicals at dangerous levels based on outdated threshold limit values that were never tested and are still in use because of corporate political pressure (219). Sealed office buildings built in the 1970s and 1980s use recycled air and have

spawned outbreaks of a new syndrome, Sick Building Syndrome (220–223), which may be a subset of MCS (221,224). Neighborhoods have become car centered. Cars have become necessary for work and pleasure, and chemicals from car and diesel exhaust, incinerators, and wood smoke turn the air in populated areas into a toxic smog (225–229). Pollution inside average urban houses with synthetic rugs, cleaners, adhesives, paints, and petroleum heating systems has increased to the point where the levels of benzene, xylene, tetrachloroethylene, and many others (230) are consistently greater indoors than outdoors, even in smog-polluted areas, by factors of 2 to 5 and often by factors of 10 or more (79). Pesticide levels indoors are commonly greater by factors of 100 compared to outdoor levels (78,79). In food, residues from many common pesticides and herbicides, as well as direct chemical additives, are eaten in the average diet (231). Many of these substances are untested or inadequately tested (232), whereas many others are already known to be toxic (231,232). As illustration, Table 2 is an excerpt showing 8 from a list of 42 commonly encountered chemicals, where they are found, and their known toxic effects. The eight chemicals shown do not appear significantly different from the unshown entries in either number of sources or overall toxicity.

People who are middle-aged today were the first generation to have encountered

these chemicals on a daily basis since birth. Because so few of these chemicals have had long-term testing, in a sense this generation is an experimental group. MCS is characterized by reactions to these chemicals, so it may be that MCS is the experimental result.

Initial Damage and Extensions. Model 2A will explore the possibility that specific configurations of increased multiple chemical exposure and stress can produce MCS through IDS interactions even though the IDSs are unchanged. In addition, Miller (90) and others (22,94) have developed models of MCS that propose sequential stages for MCS; common among these are susceptibility, sensitization, triggering, and spreading. For comparison's sake this description will adopt these stages; differences suggested by the IDS model will be discussed in "How Long is an Event?" Model 2A is shown graphically in Figure 4.

SUSCEPTIBILITY. As an example, suppose that a chronic low-level exposure (years long) to formaldehyde has created haptens and an IRA reaction in the subject (180–182). Assume that combined chronic chemical stressors such as SO_2, NO_2, and diesel exhaust particles are polluting the subject's work area simultaneously and also occurring in the subject's ambient urban air. These substances have impinged on the lung tissue (229) and a tolerance mechanism supplying compensatory lung tissue changes is occurring (20,48). Tolerance symptoms may not be noticed by the

Table 2. Some commonly encountered toxic chemicals[a] and their known toxic effects.

Chemical and where found	Toxicity in humans, including chronic and acute effects	Reference
1,3-Butadiene: rugs, rug underpaddings, rubber tires, rubber consumer products, nylon, gasoline, auto exhaust, groundwater	Leukemia, lymph cancer, blood-cell cancer; tumors of breast, bronchial tubes, stomach, large intestine, liver, heart, thyroid (in mice: testicular tumors, leukemia)	(149,233–236)
Acetaldehyde: body metabolism of alcohol; wood stoves, incinerators, smog, diesel exhaust, byproduct of Candida albicans fungal infections	DNA and chromosome damage; binds to liver and other cells, causing autoimmune responses; upper respiratory irritation, metabolic disruption, lung damage	(188,237–240)
Acetone: adhesives	Neurologic damage, lung damage; enhances carbon tetrachloride liver damage	(241)
Alkylphenol resin: carbonless copy paper (NCR forms)	Immune responses including itching/burning skin, rash, flushing, wheezing, cough; nausea; hormone (prostaglandin) irregularities	(242,243)
Benzenes (benzene, benzo[a]pyrene, naphthalene, others): gasoline (auto exhaust and interiors, gas stations), diesel exhaust, building materials, plastics, polypropylene food containers, cooked foods, printers, printed and copied paper, copy machines, incinerators, tobacco smoke, wood smoke, marijuana smoke	Bronchial, colon, and liver damage; leukemia; DNA damage; tumors including brain, liver, stomach, lung; cardiac abnormalities, eye irritation, drowsiness, unconsciousness, uncoordination, heart attack (in mice: birth defects, tumors)	(149–157)
BHT (butylated hydroxytoluene): migration from polyethylene food packaging, additive in foods (cereals, fats, meats, potatoes, others)	Allergic reactions, possible cancer, possible kidney damage (animals: behavioral changes in offspring)	(244)
Carbon disulfide: solvents, dry cleaning, painting, spray painting, glue work, varnishes	Peripheral nerve damage, emotional instability, insomnia, lessening of libido	(245,246)
Carbon monoxide: wood smoke, tobacco smoke, auto and diesel exhaust	Lung damage and irritation; carboxy-hemoglobin neutralizes blood oxygen transport	(239)

[a]This list is excerpted from a larger list of 42 commonly encountered toxic chemicals (SC Rowat, unpublished data).

1 *"Susceptibility"*
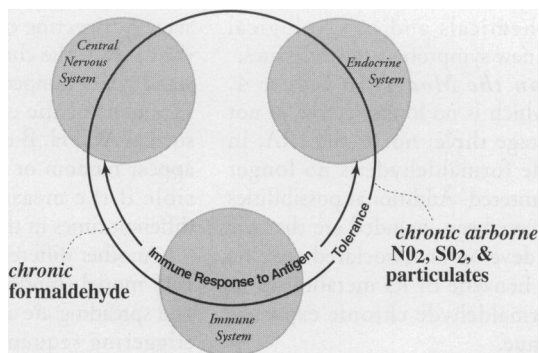
1. Chronic formaldehyde induces the immune response to antigen. Simultaneously, chronic SO₂, NO₂, and diesel and other particulate matter from air at the workplace and urban home impinge lung tissue and induce tolerance in the form of compensatory lung cell architecture.

2 *"Sensitization"*

during increased
formaldehyde
and
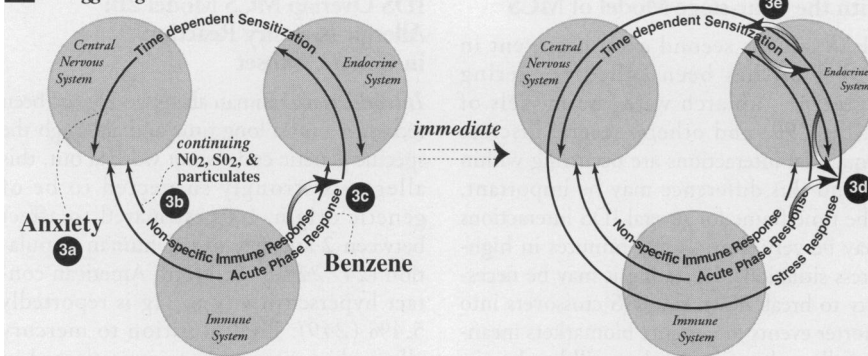**continuing airborne**
NO₂, SO₂, &
particulates
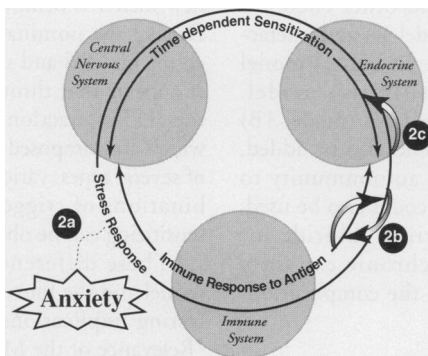
2a. Acute anxiety occurs in combination with moderately increased formaldehyde. The anxiety induces the SR.

2b. Crossover messengers interact between the SR and the IRA such as ACTH, β-endorphins, IL-1 and IL-2, and immune cells.

2c. These messengers are also involved in TDS and TDS is invoked and conditioned to recognize both formaldehyde and anxiety as inciters.

3 *"Triggering"*

3a. Later, subject encounters benzene during moderate anxiety. TDS has increased over time and is triggered by the anxiety.

3b. TDS reaction causes the already eroding lung tolerance to be breached and with continuing air pollution, the NIR is invoked to deal with cellular damage.

3c. Concurrent irritation/damage from the benzene exposure causes the APR to cascade from the NIR.

3d. Under the added influence of the TDS, the SR cascades.

3e. Multiple messenger overlaps chain the threshold for the SR to the TDS response so the SR will be invoked directly by the TDS in future. TDS also becomes conditioned to benzene as a trigger.

4 *"Spreading"*
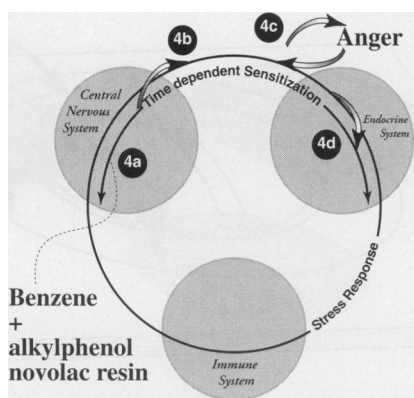
4a. Later, during moderate anger, benzene is again encountered along with alkylphenol novolac resin used in no-carbon forms. Benzene invokes TDS.

4b. TDS cascades the SR.

4c. Hormonal overlaps between the SR and anger increase anger's intensity.

4d. Messenger overlaps between increased anger, SR, and TDS cause TDS to become sensitized to alkylphenol novolac resin and anger as inciters.

4e. (Not shown.) In subsequent events this same spreading mechanism continues to add new stimulus chemicals and psychological stresses as TDS inciters.

Figure 4. IDS interaction model 2A, of MCS resulting from chemical and stress overload, adapted from the necessary stages of MCS suggested by Miller (*90*) and others (*22,94*).

subject as a pattern because tolerance mechanisms are well known for moderating the magnitude of the reaction; in a sense, that is their function.

SENSITIZATION. A strong psychological anxiety (stress) occurs in combination with a moderately increased amount of formaldehyde. The anxiety induces the SR IDS. Because of the immune response already occurring and even increased slightly because of the increased level of formaldehyde, the crossover messengers between the SR and the immune response (for example, ACTH, β-endorphins, IL-1 and -2, and immune cells, all of which are also involved in TDS) condition TDS to both formaldehyde and anxiety as inciters. Such bidirectional fertilization between psychological and chemical triggers is reported for TDS in animal experiments (3).

TRIGGERING. After some time the subject encounters a new chemical, benzene, while in a state of anxiety less severe than at the onset of the original event, so the SR IDS is not at first invoked. However TDS increases over time, even without exposures to the inciter; it is triggered by the anxiety. The tolerance mechanism, meanwhile, undisturbed during the sensitization stage, has continued to erode toward the exhaustion state (48). The added weight of the neurochemical and endocrine changes that characterize the TDS reaction causes the lung tolerance to air pollution to be breached and the NIR is invoked to deal with cellular damage that had been tolerated to that point. Under the influence of the concurrent benzene exposure, the APR is also cascaded from the NIR, and under the added influence of the TDS firing, the SR cascades. (Figure 4 shows a graphic separation of these events.) At this level of arousal TDS becomes conditioned to benzene also as a trigger, and we speculate that multiple overlaps in messengers between the TDS and the SR (Table 1) make it possible that the threshold for the SR becomes chained to the TDS response; in other words, the SR will be invoked directly by the TDS in future exposures.

SPREADING. In a later event benzene is again encountered along with a new chemical, alkylphenol novolac resin, which is used in no-carbon-required forms (242) and a new psychological stress, moderate anger. Now benzene causes TDS and hence the SR to fire, and the anger increases in intensity. The TDS becomes conditioned to both the new chemical, alkylphenol novolac resin, and to anger, the new stress, as inciters.

In subsequent events this same spreading mechanism could continue to add new stimulus chemicals and psychological stresses and new symptoms at diverse sites.

Notes on the Model. In Figure 4, tolerance, which is no longer active, is not shown in stage three; nor is the IRA; in our example formaldehyde is no longer being encountered. Additional possibilities that could have been included are that the IRA could develop an associated specific reaction to benzene or its metabolites or that the formaldehyde chronic exposure could continue.

Interactions from Other Models. In particular, pesticide and other chemical body burdens under model 1A and interactions between benzene and IL-1, model 1B, may be of interest in this model. Childhood window exposures (model 1B) and TD (model 1A) could also be added. The multiple-feedback autoimmunity to IgG model (model 1C) could also be used, say, by substituting vinyl chloride for formaldehyde as the chronic exposure agent, but at this point the complications become mind-numbing.

How Long is an Event? Comparison of IDS Models with the Four-stage Model of MCS

Although the second exposure event in model 2A has been called triggering (stage 3) to match with the models of Miller (90) and others, several discrete sequential interactions are occurring within it, and this difference may be important. The time frame for several IDS interactions may be very short; a few minutes in high-stress situations. In testing it may be necessary to break down the IDS crossovers into shorter events to measure biomarkers meaningfully; otherwise the data will be chaotic.

Figure 5 shows a superimposition of the IDS chaining during a single event, the stage-3 triggering of model 2A. Not only is the order of the chaining not easy to understand when lumped together, but any measurement of the crossed-over messengers such as ACTH, β-endorphin, IL-1, etc. will appear random or otherwise incomprehensible if the measurements are taken at different times in the triggering sequence.

Another difference is that in the current IDS model (model 2A) both sensitization and spreading are also occurring during this triggering sequence, since a new IDS is being added to the mechanism (SR) and a new inciter is being conditioned (benzene). During the nominal spreading stage, triggering of TDS and stress are also occurring. It appears that through the architecture of the IDS interaction and chaining models, which are composed of short discrete events of several types, various sequences and combinations of triggering, spreading, and sensitizing can be obtained.

These differences between the IDS model and the four-stage MCS model have testing implications that are discussed in "Relevance of the Models to Current MCS Research Recommendations."

IDS Overlap MCS Model 2B: Allergic Mercury Reaction in Genetic Subset

Introduction. Human allergy to Hg has been recognized for a long time and although the specific genetic code is not worked out, this allergy is strongly suspected to be of genetic origin. It is estimated to affect between 2 and 5% of the human population (247,248). The North American contact hypersensitivity to Hg is reportedly 5.4% (249). Predisposition to mercury allergy has recently been investigated in

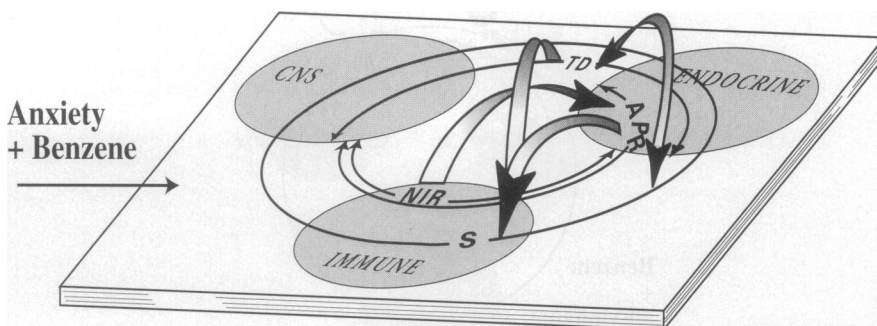**Figure 5.** Possible source of MCS biomarker data error. This graphic shows combined IDS overlap events in the level 3 triggering stage of chemical and stress overload MCS model 2A. If biochemical markers are taken indiscriminately within this period chaotic data may result, since the same neuroendocrine–immune messengers may be in use for different purposes at different times. (Figure 4 shows separated event sequence.)

genetically selected rodents. Interestingly, special rodent strains develop significant immune aberrations and autoimmune disease in Hg exposure, including exposure by implanted dental amalgam Hg configured as in human exposure (250,251).

In humans carrying dental amalgams, the amounts of Hg released have been estimated within the range that would cause reactions in those genetically susceptible to Hg (251). Therefore the millions of humans who carry Hg amalgams are theoretically at risk for genetically induced reactions. (Whether those not genetically susceptible could also be directly toxically affected by mercury is unknown; many widely divergent opinions and research reports have been published over the last few decades (247,248,251–256). Recent reports connect amalgams with oral cavity ill-health (248,257), increase in antibiotic-resistant bacteria in oral and intestinal cavities (258), multiple sclerosis (259,260), psychological complaints such as depression, excessive anger, and anxiety (261), and cardiovascular symptoms such as fatigue and high blood pressure (262).

Mercury is also available in the diet, particularly from fish. Levels of methyl mercury (MeHg) in fish appear to be growing and are a concern (263,264). An epidemiologic investigation of a fish-eating population is reported to show high susceptibility to brain damage during prenatal exposures to MeHg (263). Also Hg in paint is a widely recognized health hazard (265–267), as is skin-lightening cream (268). A syndrome of infant Hg toxicity called acrodynia is reported from application of calomel teething powders (255) and from paint exposures (267). A case–control study shows increased urinary Hg in people living in houses painted with Hg-latex paint ($p < 0.001$) (267), and a case of acrodynia occurred in a child living in such a house (267). Before 1990 one-third of the interior latex paint used in the United States had added Hg fungicide (267).

Like MeHg, Hg is toxic to the CNS and established detrimental effects range from behavioral irritability and insomnia at low levels of exposure through tremors, muscle spasms, and nerve conduction loss at higher exposure levels (253). Many other toxic effects are reported (255), including cardiovascular (262), immune (248,255), and autoimmune effects (269).

Data on a direct connection of Hg exposure to MCS is lacking except for the synchronicity of neurologic symptoms, which are the most highly reported

symptom category in MCS clinical literature and the symptoms most commonly produced by Hg. These reasons and the demographics prompted this exploratory model. Half the population of the western world has Hg amalgam fillings, and 5% may be allergic to Hg.

Initial Damage. We hypothesize a human strain that has a genetically determined immune response to Hg and a subject who has sufficient dental Hg released in the body to induce a systemic autoimmune reaction through the IRA. Subsequent to this the Hg level in the subject's body is being increased by food sources, further increasing the activity of the autoimmune response. Then a moderate-to-high exposure to toxic environmental Hg in paint, drugs, pesticides, cosmetics, or other source occurs during a stressful situation that includes a chemical exposure. For example Hg in fresh paint, in cosmetics or calomel, or in amalgam implantation in a dentist's office in conjunction with anesthetic injection or ambient chemicals might provide this combination. This exposure causes SR activation, and in combination with the ongoing autoimmunity, a combined CNS-mediated TDS to Hg and to the stress-associated chemical may begin. Because there is already an appreciable body burden of Hg and also an immune response to this Hg, there may be a messenger crossover— ACTH, β-endorphin, IL-1, or other immune cells or messengers, for example— between the TDS and the immune and SRs. This may change the threshold of response of any of these IDSs. This combined sensitization of the immune response and TDS to internal Hg may create an unstable situation that allows subsequent exposures to become conditioned inciters of the TDS during various situations; e.g., those that elicit movement or increase of the Hg body burden while stressing psychologically or chemically.

Extensions. HEAVY METALS/ZINC DISPLACEMENT. Cd, Pb, and Hg are all Zn agonists, and rising levels of Cd and Pb can add to the toxic effect of Hg in the body. Metals are unique in the environment in that they are not consumed by human enterprise and so continue to increase in the biosphere as we collect and process them (270); one review concludes that we have a growing problem of heavy metal toxicity (270). Cd is increasing in human tissue. It has a human half-life of 30 years (271) and the average human body burden since the turn of the century has increased by a factor of 4.7 according to one study

(272), with the renal concentration increasing by a factor of 47 (272). Another study found a renal increase factor of 3.8 (273). Cd is a potent developmental toxin in animal studies; its effects include CNS and behavioral dysfunctions and many others (274). Some Cd effects have been linked to its displacement of Zn from various enzymes (270,274), and Cd from maternal smoking is thought to decrease the transfer of Zn across the human placenta (275,276), which may implicate Cd in multiple teratogenic effects strongly suspected to result from Zn gestational deficiency (44,193). Pb caused a reduction in cognitive development through 7 years of age in children living in a lead-smelting community (277). Pb is also reported to cause DNA–protein crosslinks and DNA repair inhibition (270), and to accumulate in the hippocampus of children, rats, and monkeys. In monkeys the effects are accompanied by Zn displacement and learning deficits (278).

CHILDHOOD OR GESTATIONAL MERCURY EXPOSURES. MeHg exposure during pregnancy causes neurologic abnormalities, including psychomotor deficits, mental retardation, and deafness in children (279). Fetal effects occur at much lower exposure levels than required for effects in adults, although in both cases effects are almost exclusively on the nervous system, especially the CNS (268). Hg is not known to damage the fetus as heavily as MeHg, but this may be because of lack of study (253).

Combining Extensions to Produce Variants of MCS. Body burdens of chemicals, preexisting TD, early and ongoing Zn deficiency described under model 1A, and childhood window exposures and hapten spreading described under models 1B and 1C could also interact in this model. Again various subsets of the MCS syndrome might be produced depending on which of these substrates is present.

Concluding Note on Inadequate or Inappropriate IDS Models 2A and 2B. In these two thought experiments, physiologically healthy MCS subjects appear plausible through various interactions of the nine IDSs. That is, it may be that in some forms of MCS the subjects' neuro-immune–endocrine systems are functioning well—within the limits of their present design. These design limitations may now be coming to our attention because of interactions with increasing concentrations of new types of toxic chemicals and metals and possibly new levels of stress. In this model those who have MCS are at the end

of a normal distribution; i.e., they have been unlucky in how many chemicals and how much stress and heavy metal they were exposed to or in what synergistic combinations. They may have marginally different thresholds to TDS, kindling, or other IDSs than the norm. A disturbing correlate of these models is that an increasing population in the industrial world may be at risk for developing MCS.

Model 3: IDS Overlap MCS as Evolution and Learning

As discussed earlier, the immune system most likely predates the CNS. The immune system has evolved specifically as a learning mechanism. It has the function of mapping its biochemical environment i.e., to recognize and remember biochemical danger patterns (10). Partly to achieve this purpose, it is closely linked to the CNS (1,10,29–34, 42,158,280–284) and the endocrine system (10,29–31,34,158,281). Grossman et al. (10) propose that each cell is a complex feedback-controlled unit and that different cells learn to respond preferentially to different combinations of signals in their immediate biochemical environment. These signals may originate from the CNS or externally. In addition, the recent T-cell receptor recombination discoveries that make genetic encoding of specific antigens more possible (26,201,202) lead to the possibility that changes in the thresholds of various of the IDSs will be encoded genetically either within the present generation or in future generations or both. At least four different means of varying the DNA recombination code for T-cell receptors have been identified (26), and some method of saving the known toxic compounds into the germline might be an evolutionary advantage. Recent work by various researchers has pointed to adaptive genetic learning as a major possibility (201,202). In bacterial studies genetic mechanisms are reported that accelerate and direct DNA mutation during stressful situations (201).

It appears that the neuroendocrine–immune system is purposely unique in each individual, and part of this comes from experience. Jerne (7) suggests that "Early imprints leave the deepest traces."

If we consider the crossover messengers (Table 1) used by most IDS—messengers such as IL-1, ACTH, and β-endorphin, MT, mast cells, etc.—limited resources the body allocates between IDS in times of attack, we may, in a semantic reorientation, be able to model IDS threshold changes as a learning effect rather than inadequacy or

damage. It would be reasonable also if the body set these allocation ranges in advance; that may be one function of childhood windows and of neuroimmune learning in general. For instance TD can produce MPD alternative personalities that have differing immune responses (65) and many other lifelong physiologic differences; the appropriate alternative personality appears in a specific context then disappears when the context changes. Various combinations of IDSs therefore may be interacting meaningfully to adjust thresholds in readiness for special situations.

Childhood developmental windows could be understood then not only as times when toxicants can accidentally produce more damage but also as specific times when the IDSs are sampling the external environment to determine a range of response appropriate for the lifetime of a particular individual.

In a species sense MCS may conceivably constitute a healthy response to an unhealthy environment. Although MCS symptoms frequently are painful, pain can have a useful function. That is, since the chemicals MCS individuals avoid are known to be toxic in high concentrations and are also increasingly recognized as toxic and carcinogenic in chronic exposures (239,285), (Table 2), such a difference could be viewed as an improvement in the species. People who get MCS would be subject to lower rates of chemical damage and cancer because they would have an increased impetus to avoid the toxicants.

In such a model we consider it possible that it is through such IDS learning mechanisms that people with MCS have learned to abandon almost all aspects of 20th-century life that involve the smell, touch, and taste of rubbers and synthetic foams, new plastics, fresh paints, petrochemical cleaners, oil and gas fuels, and petroleum-based pesticides, perfumes, food additives, and drugs; also that their inability to be near these chemicals is probably lifelong (89). We may even imagine that persons with MCS may find themselves living in an electrically heated rugless house in a small village far from a city, with a yard bordering a wild field. When they sit in the yard on a sunny day breathing good air, listening to the birds chirping, watching their organic garden growing, and looking at the car parked in the driveway, which they can only use once a week for a 20-min trip, it may occur to them that their MCS disease—as a learning experience—might not be such a bad thing in some ways.

Testing the IDS Overlap Models

Relevance of IDS Models to Early MCS Research.
One research team investigating MCS combined masking odors such as peppermint, cinnamon, and anise with a challenge chemical so that the patient could not identify the odor of the chemical being administered (286). The author of at least one paper on MCS (287) has called for similar odor-masking studies. However odor, taste, sound, and sight—CNS perceptions—can function as conditioned stimuli (11,13). Accordingly, if MCS is a complex conditioned phenomenon, removing these stimuli may result in studies that do not find a reaction in at least some MCS patients. For instance, according to the models developed in this paper, odor may be linked in the patient's memory with acute unpleasant experiences, and by an associated IDS linkage (such as TD) may cause multiple reciprocal CNS–immune messengers [IL-1 (159,288,289), IL-6 and IL-8 (290), substance P (1,283), somatostatin (32), and VIP (33), for example] to cascade and perhaps lead to the SR (8,30,280,281,288). If such odor response is blinded, such studies could erroneously conclude that MCS did not exist.

Relevance of the IDS Models to Current MCS Research Recommendations.
If biomarker data are pursued and the interactive models developed in this paper are even partially on the right track, complex nonlinear biomarker data will be required. But how do we even know who has MCS? It has been calculated that if only 10% of a study population are responders, then to achieve a response shift of one standard deviation from norm, with $p = 0.01$ 90% of the time, the study population would need to be 2102 people, but only 23 people if 100% are responders (291). Thus, defining a small population of people with MCS in the absence of reliable biomarkers is a catch-22. Perhaps long-term self-control crossover studies (291,292) that can measure data at various points in the triggering–spreading sequence would be more useful, but the number of such studies that could be economically carried out in a limited timeframe is small. Also there is no way to know if we are measuring people with MCS or people who are willing to spend time in a physician's office.

Recent research groups working on MCS testing (84,293) recommend using only people who have had a verifiable single-exposure event precipitating their MCS. But how representative of the entire population is this? Not only do we not

know how many gradual onset cases are being left out, the crossover with chronic fatigue and fibromyalgia, among other conditions, is reportedly high. These conditions may even be indistinguishable in most cases (*89*). If it turns out that an IDS model accounting for all these effects simultaneously is required—perhaps what Miller has called "an emerging category of disease" (*294*)—then limiting studies to only a small number of adult single-event precipitated MCS cases in a clinical setting may seriously decrease our knowledge base for building the pattern.

An additional serious problem with clinical testing discussed in "Working Definition" is that some of the IDS models developed in this paper predict that people with MCS will have psychological reactions in a testing situation, which will distort results. Conversely they may require a particular type of psychological stress to produce their reaction, and such stress may only occur when they are in their ordinary life settings. Bell et al. (*86*), in their working-group report on MCS testing, referred to the need to avoid novelty in testing situations (a variant of this same problem) and concluded, "it will be essential to perform multiple, not one exposure sessions separated in time....That is, it is necessary to initiate and elicit sensitization within the same experiment." This is an important limitation and may be difficult to achieve. Cohen et al. (*293*), in another working group, state the problem clearly: "Do events perceived as stressful in the recent or past history of the individual play roles in the onset and/or progression of MCS? ...Which factor is more important in the traumatic initiation: the exposure to chemicals associated with the traumatic event, and/or the stressful experience associated with the event? Can a stressor precipitate MCS in a chemically sensitized individual who is not displaying overt symptoms of MCS at the time of stressor exposure?"

Yet their recommendations on the design of controlled exposure studies (*293*), according to my interpretation, do not circumvent this. In making recommendations on testing three other working groups from the same conference (*77,84,295*) made no reference to this problem, yet it seems crucial.

Animal studies may help clarify the situation. The Bell et al. (*86*) working group suggests a series of experiments on rodents with each series taking measurements from microelectrode bundles in the brain. The series roughly measures: *a*) chemical odor only, *b*) stress first, then chemical odor,

and *c*) chemical odor first, then stress. This allows the use of stress, which the human model does not. It does, however, leave out variables explored in some of the IDS models; for example, it has no simultaneous stresses and chemicals and no provision for combinations of early developmental windows, body burdens of chemicals and metals, gestational and chronic Zn deficiency, or a genetic allergy. These variables could be added in future experiments, but finding the right combination(s) might be time consuming and possibly even prohibitive in nonhuman subjects.

Also there is the problem outlined in "How Long is an Event? Comparisons of IDS Models with the Four-stage Model of MCS" that several very short IDS-chaining events may be being lumped together under what is nominally called sensitization, triggering, or spreading. Additionally, these events may constitute combinations of sensitization, triggering, and spreading and even more importantly may use identical messengers that perform changing functions within very short time spans. Unless the measuring protocol is programmed for such shifts, chaotic biomarker data could result.

Rigorous double-blind (*84*) and balanced-placebo design (*295*) clinical testing suggested by some work groups may be critical in convincing other investigators, doctors, and legislators of the legitimacy of MCS as a debilitating condition, and should probably be undertaken immediately. But these tests may not identify the origins of MCS. An analogy is that for a century it has been possible to view the symptoms of MPD or BPD in clinical settings and the disorders have long been accepted as valid. Yet only recently has a convincing etiology been discovered (*57,58,60,65,66*); this has been through collating large numbers of patient questionnaire self-reports. These early traumas were not available in clinical settings to either the people who experienced them or the health care workers who had not.

Identifying MCS Mechanisms by Large-scale Self-report Epidemiology. An alternative investigation route that appears logical is large-scale self-report epidemiology of MCS. After decades of argumentative discourse among the medical profession and the press, people with MCS are aware and beginning to get organized, even if they do not congregate in cities or at conferences. They act most frequently through newsletters and memberships in local self-help organizations. There are many national organizations and newsletters,

especially when the associated conditions of fibromyalgia and chronic fatigue are considered. It is possible that by using e-mail and the telephone, 10 organizations could quickly be found that would each provide addresses for 500 persons. Within a short time, a mailing could be sent to 5000 people, all of whom had self-defined long-term MCS. This mailing could be done either at the same time as or in advance of animal and clinical studies called for by the research groups working on MCS.

One suggestion might be for each member of a panel of six to eight people who have been studying this condition for many years to produce 50 to 100 questions based on his or her work. These questions would then be collected, sorted, and culled to a workable number—perhaps 150 questions. These questions would be mailed, returned, and statistically analyzed for useful patterns that might suggest directions for future testing and research.

It appears appropriate to suggest that at least one panel member prepare questions based on the IDS interaction models. It also seems reasonable to have at least one panel member with overt MCS symptoms and who has lived with MCS for an appreciable period of time. This might expand the functional perspective of the panel; and help validate the undertaking for those approached to contribute addresses and contacts as well as those asked to complete the questionnaire. It would also be important that at least one panel member have previous experience with wide-area questionnaire preparation, distribution, and analysis. Finally, including some carefully designed open-ended and single- and multiple-choice types of questions might allow more robust cross-checking of the data. This has recently been demonstrated in a long-term questionnaire study searching for developmental correlates in an adult population (*296*).

Conclusion

Available evidence is consistent with a category of disease that develops through the interaction of existing human IDSs. Three models of such IDS disease generation are suggested: damaged IDSs, inappropriate or inadequate IDSs, and evolving or learning IDSs.

Several nonexclusive mechanisms of MCS based on these IDS models appear plausible. If one or more of them are accurate, demonstrating the existence of MCS and verifying its mechanisms may involve a simultaneous study of clinical, animal, and large-scale self-report data.

Appendix

Additional Descriptions of IDSs: Mode of Action and Inciters

Definitions and range of physical response for each IDS are discussed in "Integrated Defense System Overlaps as a Disease Model." Table 1 lists the IDS models with range of physical action and inciters.

Time-dependent Sensitization

Mode of Action

In animals, when one or more noxious chemicals or stresses are encountered above a certain threshold level through any body exposure route, responses related to survival (297) occur in the CNS, endocrine, and immune systems. Later when this same stressor is encountered, this response has increased (sensitization) or other stressors or chemicals are now sensitized (spreading). Intermittent stress encounters prolong or increase sensitization; continuous ones may induce tolerance (3,22). TDS sequelae in humans have been suggested to include paranoid schizophrenia, panic disorder, PTSD, and MCS. Associated neurologic changes appear to be irreversible. TDS has been postulated to be "...dependent on changes or alterations in gene expression" (298). Behavioral and neurochemical responses of genetically different rats showed significant differences in the development of TDS (297); hence, human host susceptibility to TDS may differ appreciably with different inciters or mediators.

Inciters

There are many chemical and nonchemical stressors. Chemicals include: amitriptyline, amphetamine, haloperidol, ethanol, IL-2, nicotine, and corticosterone. Nonchemical stresses include immobilization, shock, syringe insertion and withdrawal, saline injection, and time in a strange environment (3).

Immune Response to Antigen

Mode of Action

Description of the antigen-specific immune response to follow is highly simplified, partly because of the "virtual explosion of information that has taken place within the field of immunology" (2) in recent years and partly because the immune system is so closely complexed with the central nervous and endocrine systems.

In brief the specific immune response has the important characteristics of long-term memory through memory cells and probably genetic coding; tolerance through suppressor T cells that modulate other immune functions; and associative spreading of the response by recognition of multiple epitopes on one antigen, and possibly by other mechanisms such as CNS-mediated conditioned learning.

T lymphocytes are activated by antigen presented to them by macrophages or other presenter cells, and in turn they grow, multiply clonally, and begin expressing molecular messengers that in turn activate B cells, other T cells, and other types of cells to aid in attack and other responses to that specific antigen (2). Many of these messengers communicate directly with receptors in the endocrine organs or on CNS cells (32), so the response can involve all body systems even if the antigen is local. The immune responses can in turn be modified by input from the CNS and endocrine messengers. In addition an autoimmune T-cell-mediated response is sometimes mounted against the host's own tissue. This can occur when the tissue is complexed with a foreign antigen or for other unknown reasons.

A major discovery of recent years is that antigen-specific memory T cells, which will precipitate a faster, stronger response on second encounter with the antigen than naive T cells (203) and B cells, can sometimes persist for a lifetime (203) without any intervening booster encounters with the original antigen (5,299).

Another important recent discovery is that the antigen-recognizing T-cell receptors undergo directed gene rearrangement early in T-cell growth in the thymus (26,28). Thus, it appears possible that antigen recognition is being genetically encoded (201,202), although such a feedback loop has not been characterized in detail.

Inciters

Inciters include bacteria, fungi, and viruses, other foreign tissues, self-tissues in autoimmune reactions, chemicals such as phenol, alcohol, formaldehyde, toluene diisocyanate, PCBs, and polybrominated biphenyls, metals such as Hg and nickel, and messengers from the nervous and endocrine systems including those induced by psychologic or physical stresses.

Kindling

Mode of Action

Kindling was the name given the effect observed when brief applications of same-strength electricity to the brains of animals produced stronger and stronger reactions—from no reaction through electroencephalogram changes to full convulsions even after stimulation had stopped (4). Partial kindling produces behavioral changes secondary to brain chemistry changes, and in humans chemical partial kindling has been used to explain lasting panic disorder and anxiety (22). Behavioral changes secondary to kindling have been postulated to result from the major part the limbic system plays in controlling survival activities.

Inciters

Various chemicals evoke a kindling response in humans (22). These include cocaine, amphetamine, β-endorphin, lidocaine, physotigmine, and the pesticides lindane and dieldrin. After initiation physical stressors and morphine have been noted to be inciters (22).

Nonspecific Immune Response

Mode of Action

The so-called innate (39,161) immune system can be viewed as any first-line immune reaction to an unanticipated pathogen. The first contacts include mast cells, NK cells, collectins such as MBP, macrophages, T cells, and B cells. After contact with pathogenic bacteria, fungi, viruses, lectins, or superantigens (162) or after stimulation by neuropeptides such as substance P (1), various mediators are expressed to produce cascading reactions, including proliferation of the original cells. For instance, mast cells produce TNF-α, IL-1, IL-3, IL-4, IL-6, GM–CSF (40), and histamine (1), which have multiple effects on T, B, and other immune cells and on receptors in the nervous and endocrine systems, whereas MBP induces complement-mediated responses such as killing of bacteria (39).

Inciters

NIRs are elicited by such factors as microorganisms (bacteria, fungi, viruses); lectins from a wide range of plants, animals and fungi, some of which are common in the diet (peanut, wheat germ, potato, tomato, various legumes, and others); exogenous

superantigens such as staphylococcal enterotoxins (*162*); endogenous super-antigens (*162*); chemicals such as phenol resins (*242*) and dimethyl sulfoxide (*300*); and neuropeptides such as somatostatin, substance P, and VIP (*32*). Stress suppresses nonspecific T-cell proliferation (*14*).

Acute-phase Response
Mode of Action

Tissue damage or infection (as opposed to a psychological stress; see "Stress Response") causes principally macrophages, platelets, and blood monocytes but also mast and other cells to release cytokines such as IL-1 and TNF, which have both local and distant effects (*41,289*).

Locally a second wave of cytokines is released by stromal cells, and local endothelial cells undergo changes that induce leukocytes into the tissue. An arachidonic acid cascade occurs, including prostaglandins and thromboxanes, and vascular tone changes occur, swelling and redness, for example. Histamine, serotonin, and platelet-activating factor change tissue flow of fluids. Pain occurs through molecules such as bradykinin, which are released during clotting (*41*).

Distantly the interleukins and TNF can have multiple effects (*29,158,288*), including changing the hypothalamic temperature setting (fever) and inducing changes in liver metabolism. Distinct sets of acute-phase proteins are induced separately in the liver by IL-1 as opposed to IL-6-type cytokines (*41*); the former include glycoprotein, C-reactive protein and complement C3, the latter include fibrinogen and antiproteases (*41,288*). Liver changes also include production of MT and the consequent lowering of plasma Zn levels (*44,138,301*).

These cytokines can also induce ACTH from the adrenal–pituitary axis, generating corticosteroids that feed back to suppress the immune reactions (*6,41*); this can be accompanied by direct production of analgesic β-endorphins by B cells (*31*). At this point the CNS is directly involved, as CRH can be induced in the brain by interleukins and psychological stress (*281*), and it induces ACTH and hence corticosteroids. This description merges with that of the SR described below.

Although it may be that the APR diminishes by an undirected erosion over a 24- to 48-hr period, it is also reported that IL-4 and IL-10, produced by some T cells, can accomplish downregulation of IL-1, IL-6, and IL-8 (*41*).

Inciters

Physical tissue injury and infection by microorganisms are described as primary inciting mechanisms (*41*). Based on Zn/MT fetal damage studies, induction may also occur through contact with toxic environmental chemicals such as urethane, ethanol, and others (*44,192*).

Stress Response

Mode of Action

Coordinated responses take place when a systemic threat is perceived. This perception may be triggered through release of immune mediators such as IL-1, IL-2, IL-3, IL-6, TNF, and prostaglandins (*6,281*) resulting from a local injury, trauma, or infection or it may be induced centrally first, by psychological stress (*281,302*) for example.

With central perception of stress, several feedback loops are invoked within the neuroendocrine–immune system; the interactions between these, although complex, presumably determine how the response occurs, its intensity, and how long it lasts (*31,281*).

The main functional changes are energy redistribution toward improved attention and alertness and suppression of less essential behavior such as feeding and sexual interest (*6*). The brain, certain muscles, and other organs of immediate need are supplied with more oxygen and nutrients (*6*).

The immune response is also significantly suppressed at various levels (*6*). This has been well documented (*29,32, 281,303*) and includes cells (macrophage, T, B, NK, etc.) and downregulation of cytokines such as IL-1, IL-2, and others (*304–306*). Less research reports differential effects, with some immune parameters showing increased activity (*303*); this may be time dependent (*305*).

The main effectors are corticosteroids and catecholamines; the former have been more extensively documented and are presumed to be centrally induced, although this may prove not to be true with the advent of newer evidence. CRH, induced in the brain by stressors (including interleukins) induces ACTH from the pituitary and thus corticotropin from the adrenal gland. CRH is associated with SR behaviors such as anorexia, decreased libido, and motor activity changes. Fear responses and decrease in willingness to explore have been reported at higher dosages (*6*).

CRH also induces—and is induced by—the central autonomic arousal system

(norepinephrine), resulting in simultaneous expression of catecholamines, which contribute, with the glucocorticoids, to both behavioral and immune effects.

Inciters

SRs may be elicited by immune-mediated infection, physical trauma, the APR, psychological trauma, drugs (*297*), environmental chemicals, muscular exercise, cold (*48*), solar radiation (*48*), and natural and synthetic estrogens (*48*).

Neurogenic Switching
Mode of Action

A recently named hypothesis by Meggs (*46,307,308*) explains how antigen, stress, chemical exposure, or damage at one body site might lead to diverse symptoms at multiple distant sites. Anaphylactic reactions and food-allergy symptoms are some suggested end products.

On the one hand mediators such as IL-1 and IL-2 participating in IgE and other immune responses also affect the release of neuropeptides such as substance P from nearby nerve cells. On the other hand, substance P, a known participant in neurogenic inflammation caused by chemicals, also can incite the IgE response and cause other immune changes. Thus a feedback loop can be initiated.

Although not using the term NS, another review (*32*) has shown how this could happen in the intestines, where neuropeptides substance P, somatostatin, and VIP are produced by nerve cells, received by various immune cells, and produced by various immune cells.

Because we know the CNS can be conditioned to control immune responses (*10*), for instance to have an audiovisual signal control IgE response to egg albumin in the intestines (*13*), and that immune responses can quickly become systemic reactions that include CNS modulation (such as in anaphylactic shock after insect bite), this feedback loop of cross-communication between adjacent nerve and immune cells has been suggested to be a likely candidate for explaining such puzzling conditions as migraine, asthma, arthritis, and MCS (*46*).

Inciters

Almost any exogenous or endogenous agent recognized by the immune or peripheral nervous system or by higher CNS processing centers may be involved. This includes such factors as stress, chemicals, foods, organisms, and self-proteins.

Tolerance

Mode of Action

Tolerance corresponds to stage 2 (resistance) in Selye's well-known three-stage general adaptation syndrome model for response to chronic stressors (48). Stage 1 is alarm reaction, which corresponds to a combination of the APS and SR described above and stage 3 is exhaustion where the organism has lost its ability to defend by adapting and unregulated damage is occurring.

Because an overall mechanism for the induction of tolerance has yet to be postulated, we remain at the descriptive stage. However tolerance is so widely reported in human and other life-form responses to various insults that it may be useful to define it as being any back-up system developed by an organism that allows it to more successfully bear a chronic injury.

Tolerance eventually gives out. In other words all of the forms of tolerance described below—with the possible exception of certain forms of nonpathogenic food tolerance (49)—delay or minimize damage but eventually succumb to a long-term chronic stressor. During this process of succumbing (exhaustion) (48) systemic changes occur; e.g., rat lungs may lose tolerance to NO_2. Stephens et al. (20) describe this process as follows "...pathogenesis continued to produce additional alterations at various biological levels, first stepwise and then simultaneously, and so become identified at some point as a 'clinical entity'...It appears that adaptation may not be sustained in the face of persistent stimulation from an injurious agent...."

Reported examples of tolerance include changes in *Escherichia coli* colony-forming when treated with Cd (309); in rat lung tissue repair in response to NO_2 (20) and

gasoline (310); in human psychophysiologic responses such as body balance and reaction time to inhaled xylene (311), ozone, and various solvents (53); and in response syndromes to Zn oxide fumes, nitroglycerin, and cotton and other grain dusts (47). One review of examples (47) imputed to tolerance and its interruption tells of: brain- and CNS-mediated behavioral effects; asthma; an infectionlike syndrome that includes fever, coughing, nausea, and weakness; a syndrome with drowsiness, severe headaches, and vomiting that sometimes includes violent behavior; a syndrome with airway irritation, coughing, pulmonary function test reductions and red blood cell fragility; emphysemalike changes and fibrosis; olfactory fatigue; and excess stimulation and tiredness in an alternating pattern (indicating repeated tolerance interruption).

A special type of tolerance has been proposed for the immune system; various cells such as T and B cells are widely believed to function by suppression (7,55) and anergy (54), which are forms of self-controlled tolerance. Yet another form, food tolerance or intolerance, also involves the immune system, including the immuoglobulins, but may be distinct since it has some unusual features (49). Addiction, including food addiction (312), has been described as an unfortunate type of tolerance (47,52); in this case, the organism procures and self-administers the insulting agent to enjoy certain aspects of the tolerance mechanism (52) or to ensure that tolerance continues (47,312).

Masking and masked addiction are terms applied to the inability of a self-conscious organism to know the inciting agent (78). It occurs during tolerance when the exposures are continuous and the

symptoms are diffuse. It can occur for foods (312) and it has been proposed that masked tolerance to household chemicals is a significant unrecognized health problem (313).

At least one tolerance mechanism is described as proceeding by adaptive changes in DNA transcription (309). Possibly the recent change of scientific paradigm (still under debate) that allows for directed genetic adaptation (28,202) as opposed to merely random mutation will stimulate our understanding of other DNA mechanisms of tolerance if these exist.

Tolerance mechanisms have been suggested as an underappreciated reason why dose–response curves are frequently nonlinear (51).

Inciters

Possibly any chronic stress can evoke tolerance responses. Examples reviewed (47,51,52) and reported to induce tolerance include diverse inhaled chemicals and particle dusts including cotton and grain dusts, ozone, xylene (311), NO_2 (20), nitroglycerin, systemic lead and cadmium, welding fumes from Zn, copper, magnesium and aluminum, solvent fumes from paint, varnish, adhesives, pesticides, and cleaning solutions, caffeine, cigarette smoke, narcotics, cocaine, marijuana, alcohol, formaldehyde, gasoline (310), gas combustion products, and continuously consumed allergenic foods (312) such as corn, milk, eggs, wheat, beef, pork, and citrus fruit, and immune-defined antigens such as infectious microorganisms and dietary lectins (54).

Traumatic Dissociation

TD is described in full in "Integrated Defense System Overlaps as a Disease Model" under "Traumatic Dissociation."

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