CHEMICAL SENSITIVITY

A Report to the New Jersey State Department of Health

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This report was developed as part of the New Jersey State Department of Health's on-going examination of the issue of chemical sensitivity. Distribution of the material does not constitute an endorsement of its content by the New Jersey State Department of Health.

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PREFACE

Given the current controversies concerning the nature of chemical sensitivity and the fact that many physicians and scientists doubt its existence to be physical in origin, some words of explanation are in order for the reader of this report. At the beginning of the report, we describe patients who claim to be "chemically sensitive" -- i.e., who claim to suffer acute adverse reactions to low levels of chemicals commonly found in homes, schools, places of employment, and other environments. In the ensuing pages, we drop the quotation marks and avoid use of terms such as "allegedly affected individuals" because their continual use would be awkward. Sufficient "proof" is not available to satisfy the most skeptical critic that chemical sensitivity exists as a physical entity; nor is there convincing proof that it does not. We, however, are persuaded that the collective evidence, in part anecdotal and in part based on good scientific studies, does present a sufficiently compelling case to warrant further study. We can not assert that millions of people are affected, although exposure to many chemicals is ubiquitous and is expected to continue. The size of the public health problem is unknown, but the scale of potential exposure suggests that the problem could be significant. We ask that the reader approach this report with an open mind and withhold judgment on these issues until he or she has read the entire report. A more focused second reading might also be needed.

The report has been critiqued as a result of a formal broadly-based review process undertaken by the New Jersey Department of Health. We have also solicited reviews from those colleagues whose opinions and scholarship we highly value. The responses were constructively critical; they will provide helpful guidance in the preparation of a manuscript for future publication based on this report.

Some criticism, while important, was based on a misunderstanding of the purposes of the research which were: (1) to clarify the nature of chemical sensitivity and (2) to identify ways the New Jersey Department of Health can assist those who are affected. In undertaking this task, we reviewed much of the available scientific and medical literature relating to low-level chemical exposure and resulting disease. We also interviewed key individuals in various medical disciplines including allergy, clinical ecology, and occupational medicine. We found scientific and clinical evidence to support plausible hypotheses concerning this disorder. The evidence also offers fruitful areas for further research. In addition, we found areas of significant interprofessional conflict as well as areas of agreement. We noted an increasing desire by all parties to find a common ground from which the issues can be objectively and cooperatively addressed.

Much, but by no means all, of the anecdotal evidence for chemical sensitivities has been reported by clinical ecologists -- physician practitioners whose clinical practices have come under intense criticism. Some reviewers chided us for not giving more critical review of questionable clinical practices. This was not our purpose. Other critics thought we should have eliminated all critical references to allergists as well as to clinical ecologists. Overall, we sought to avoid recounting the interprofessional disagreements between allergists and clinical ecologists. Chemical sensitivity is by no means the exclusive property of clinical ecology. Occupational and

environmental medicine contain sufficient examples to suggest a real medical problem. Our focus was on the problem of chemical sensitivity, not on the history of interprofessional conflict surrounding clinical ecology.

Some reviewers were concerned that the lack of sufficient data in this area rendered our conclusions speculative and hence biased. Certainly there is speculation in the report. However, there is a difference between constructing rational hypotheses concerning the existence of chemical sensitivity based on all the evidence and engaging in unfounded conjecture.

Finally, some questions have been raised as to our heavy emphasis of the importance of the environmental unit in addressing the problem of chemical sensitivity. The unit is essential for documenting the existence of the problem for research purposes. In a minority of patients, the unit is necessary for diagnosis. For others, avoidance of exposures and testing on an outpatient basis may be sufficient.

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EXECUTIVE SUMMARY

INTRODUCTION

Chemical exposures are endemic to our modern industrial society. Increased production/use of organic chemicals and advances in consumer products and building construction have resulted in changes in the nature and extent of human exposure to chemicals. Most patients who believe they are chemically sensitive initially seek medical care and consideration from traditional medical practitioners, many of whom are ill-equipped or reluctant to provide the painstaking and time-consuming attention that is required for their condition. In their attempts to obtain help, these "chemically sensitive" patients find themselves caught up in an acrimonious cross-fire among several different groups of physicians--traditional allergists; clinical ecologists; and in some cases, ear, nose, and throat specialists, occupational physicians, and others. This acrimony is fueled by different medical paradigms of the definition, diagnosis, and treatment of disease or symptoms associated with exposure to low levels of chemicals in food and water, the outdoor environment, the work environment, indoor air, and consumer products. Legal conflicts further complicate the associated scientific and medical differences. Attempts by "chemically sensitive" persons to obtain workers' compensation, disability payments, and damage awards from employers and from the producers and users of chemical products result in an adversary system which draws medical practitioners unwillingly into the center of the conflict. Further exacerbating the situation are the insurance industry and employers who seek to reduce the escalating costs of medical care in general.

This report was commissioned by the New Jersey Department of Health in order to clarify the nature of chemical sensitivity and to identify ways in which a state department of health can assist the chemically sensitive person and disengage the patient from the cross-fire described above and its attendant conflicts. In undertaking this task, we reviewed much of the available scientific and medical literature relating to low-level chemical exposure and resulting disease. We interviewed key individuals in various medical disciplines including allergy, clinical ecology, and occupational medicine. Physicians involved with the chemically sensitive patient are concerned about being drawn into a legal and political struggle that ultimately may not help the patient. Through our interviews we were able to identify not only areas of conflict between the allergists and clinical ecologists, but also unexpected areas of common ground.

We are at a critical crossroads. There is at this time a small window of opportunity which may be closed if we do not take action to address the problems of the chemically sensitive individual in a caring and equitable way. The recommendations made in this report result from our interviews, literature review, and examination of the issues, and we suggest that their adoption is necessary for making substantial progress in this area.

The reader is cautioned that this executive summary is not an adequate substitute for the entire report. The subject is complex and requires more explication that a brief summary can provide. Below we present essential material excerpted from the various sections of the full report.

SENSITIVE POPULATIONS AND LOW-LEVEL EXPOSURES TO CHEMICALS

A review of the literature on exposure to low levels of chemicals reveals four groups or clusters of people who may be chemically sensitive:

(1) Industrial workers

(2) Occupants of "tight buildings," including office workers and school children

(3) Residents of communities whose air or water is contaminated by chemicals

(4) Individuals who have had personal and unique exposures to various chemicals in domestic indoor air, pesticides, drugs, consumer products, etc.

These four groups are listed for comparison in Table I. While these groups differ in professional and educational attainment, age and sex, and the mix and levels of chemicals to which they are exposed, all have multiple symptoms involving multiple organ systems with marked variability in type and degree of those symptoms. Symptoms are often "subjective." For example, central nervous system (CNS) symptoms such as difficulty concentrating or irritability are common and physical examinations are frequently unremarkable for individuals in each category. Careful analysis of these groups may reveal differences that can illuminate the etiologies and suggest effective therapeutic options for the myriad problems comprising chemical sensitivity. These differences also may create a referral or selection bias such that members of the four groups present themselves preferentially to different medical practitioners, e.g., some may consult occupational health physicians, others primary care physicians, and still others clinical ecologists or allergists.

Symptoms experienced by people in tight buildings, by industrial workers in a particular workplace, or by the residents of a contaminated community occur within a relatively short time period--perhaps within weeks or months. These symptoms may occur after a recognized event, such as the installation of new carpeting, relocation to a new workplace, or changes in workplace or community exposures. The "temporal cohesiveness" of exposures and symptoms can contribute to the recognition of the problem as real. Acceptance of chemical sensitivity as bona fide physical disease may also be facilitated by the recognition that it is widespread in nature and is not limited to what some observers would describe as malingering workers, hysterical housewives,

Table I
CHEMICALLY SENSITIVE GROUPS

	Nature of Exposure	Demographics
(1) Industrial Workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20 to 65 years old
(2) Tight Building Occupants	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white collar office workers and professionals; 20 to 65 years old; school children
(3) Contaminated Communities	Toxic waste sites, aerial pesticide spraying, ground water contamination, air contamination by nearby industry and other community exposures	All ages, male and female; children or infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
(4) Individuals	Heterogeneous; indoor air (domestic), consumer products, drugs and pesticides	70-80% females; 50% in 30 to 50 year age bracket [Johnson 1989]; white, middle to upper middle class and professionals; farmers

and workers experiencing mass psychogenic illness. We are struck by the fact that individuals in such demographically divergent groups as industrial workers, office workers, housewives, and children, report similar polysymptomatic complaints triggered by chemical exposures.

Patients suffering from multiple chemical sensitivities may be exhibiting a non-classical and non-atopic (i.e., non-allergic) type of sensitivity. Their health problems often (but perhaps not always) appear to originate with some acute or traumatic exposure, after which the triggering of symptoms and observed sensitivities occur at very low levels of chemical exposure. The inducing chemical or substance may or may not be the same as the substances that thereafter provoke or "trigger" responses. (Sometimes the inducing substance is described as "sensitizing" the individual, and the affected person is called a "sensitized" person.) Reactions may sometimes be observed at incitant levels similar to those to which classically sensitive and atopic patients respond. However, unlike classical toxicity, the effects of low-level exposures are not simply those effects observed in normal populations at higher doses. The fact that normal persons, e.g., most doctors, do not experience even at high levels of exposure those symptoms that chemically sensitive patients allege they have at much lower levels of exposure probably helps explain the reluctance of some physicians to believe the problems are physical in nature. [While this also describes atopy (allergy), here the sensitivity is not IgE mediated.] To compound the problem of physician acceptance of this illness, multiple organ systems may be affected and multiple substances may trigger the effects. Over time, there seems to be a spreading of sensitivities, both in terms of the types of triggering substances and the systems affected. Avoidance of the offending substances is usually effective, but much more difficult to achieve for these patients than for classically sensitive patients, since the problems may occur at extremely low doses and the exposures may be ubiquitous. Adaptation to chronic low-level exposure with consequent "masking" of symptoms may make it exceedingly difficult to discover these sensitivities and unravel the multifactorial triggering of symptoms.

The fact that sensitivity means something quite different to toxicologists, allergists, and clinical ecologists reflects the different disease paradigms under which each operates. Neither traditional allergists nor toxicologists fully appreciate the two step process, induction and triggering, that seems to characterize multiple chemical sensitivities.

Those clinical ecologists who reference the literature on classical chemical toxicity to buttress their case for chemical sensitivity may be adding to the confusion and may be contributing to the reluctance of others to accept their ideas. Likewise, allergists who dismiss chemical sensitivity on the grounds that it is not consistent with the IgE-mediated sensitivity they know best may be overlooking another kind of sensitivity in their patients. While chemicals may act in some manner to predispose or cause the body to be reactive to subsequent low-level chemical exposures, this latter effect, i.e. hyper-reactivity to low levels of chemically diverse and unrelated substances, is not toxicity as classically defined or understood at this time.

MAGNITUDE AND NATURE OF THE PROBLEM

Chemical sensitivity presents a challenging puzzle for the scientist, physician, and public policy decision-maker. The pieces of the puzzle include (1) observations of possible offending or triggering substances and health effects, and (2) plausible mechanisms, diagnostic approaches, and therapies. While a definitive and accurate picture is yet to come, at this time the pieces--viewed collectively--provide sufficient evidence to conclude that chemical sensitivity does exist as a serious health and environmental problem and that public and private sector action is warranted at both the state and federal levels. Just how large a problem exists is not known at this time. The National Academy of Sciences has suggested, without providing documentation, that approximately 15% of the population may experience "increased allergic sensitivity" to chemicals [National Research Council 1987]. Our review of the existing evidence suggests that chemical sensitivity is increasing and could become a large problem with significant economic consequences related to the disablement of productive members of society.

Critics of chemical sensitivity argue that the alleged disease[s] suffers from the lack of a uniform case definition. With the multitude of environmental exposures (both chemical and food) that allegedly can result in a seemingly endless array of physical and mental syndromes and the frequent absence of findings on routine physical examination, practitioners who see these patients are at great disadvantage in trying to diagnose the condition.

To circumvent this problem, we propose the following operational definition of multiple chemical sensitivity, a definition that is based upon environmental testing:

> The patient with multiple chemical sensitivities can be discovered by removal from the suspected offending agents and by re-challenge, after an appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge.

For research purposes, challenges should be performed in a double-blind placebo-controlled manner. However, as will be discussed below, we are not recommending use of an environmental unit for all patients.

The above definition embodies an approach to uncovering environmental causation that was developed by Dr. Theron Randolph. Randolph originated the idea of an environmental unit employing what he terms "comprehensive environmental control" as both a diagnostic and therapeutic tool for dealing with these patients. Briefly, this technique involves placing the patient in a specially constructed environment devoid of materials that off-gas, avoiding the use of drugs, cosmetics, perfume, synthetic materials, etc., and having the patient fast for a period of days until

symptoms resolve. This initial period of avoidance and fasting requires approximately 4-7 days on the average. At the end of this time, the patient's symptoms, if environmentally related, should clear. At the end of this avoidance phase, the patient generally has a markedly lower pulse rate and an increased sense of well-being as well as resolution of symptoms. Next, individual foods are reintroduced, one per meal, and the patient is placed on a rotating diet of "safe" foods (i.e., foods that did not provoke symptoms for that particular patient). Drinking waters from a variety of sources also are tested to find one most compatible with the patient. Finally, the patient is challenged with very low levels (levels routinely encountered in daily living) of common chemicals. Those exposures, both food and chemical, which induce symptoms are to be avoided.

We feel strongly that this operational definition is essential to resolving, once and for all, the debate whether an individual's symptoms are or are not environmentally induced. An environmental unit is necessary for scientific validation of the concept of chemical sensitization. Because of the expense and time required by patients and physicians alike, we are not arguing that the unit be used for all patients. Nor are such stringent measures necessary for most patients. However, for severe cases there is no alternative at present, and it is only from first-hand observation of hospitalized patients that physicians will have the opportunity to understand this illness better. (This argues for the establishment of [a] demonstration unit[s].) In time, as more clinical data on these patients accumulate, physicians may be able to diagnose this disorder on the basis of the patient's history and a few key laboratory tests. For now, reliance must be placed on rigorous study in an environmental unit.

The environmental unit is the gold standard against which all other diagnostic approaches and screening techniques should be measured. However, most individuals can remain outpatients while they are guided through an elimination diet, avoidance of possible chemical incitants and rechallenge with suspected offenders. An environmental unit is necessary in more severe cases, e.g., those who have failed outpatient attempts at management or for patients with seizures, suicidal tendencies, arrhythmias or other problems requiring continuous vigilance. In this report we discuss provocation-neutralization and other office-based techniques, some lacking scientific verification, that have been adopted by clinical ecologists in order to screen for and treat this illness.

One of the keys to understanding chemical sensitivity is the complex concept of adaptation. Understanding adaptation is important here for two reasons: (1) adaptation makes it difficult to discover the effects of a particular exposure on the body and (2) chemical exposures may adversely impact adaptation mechanisms thus leading to illness. Adaptation to an enormous range of substances has been noted. These may be divided into five major subgroups: (1) outdoor air pollutants; (2) indoor air pollutants, both domestic and workplace; (3) food contaminants and additives; (4) water contaminants and additives; and (5) drugs and consumer products. In this report we review the literature on these substances as possible causes of a variety of diseases. However, by presenting this material we are not affirming an environmental

cause for these diseases, but hoping to alert the reader to that possibility and the need for evaluating such patients in an environmental unit when more traditional approaches have failed. What might seem obvious--that foods and chemicals are not significant factors in most of these disorders--could change if one were to eliminate masking and control for the effects of adaptation.

We cannot overemphasize the important distinction between recognizing the existence of a disease and knowing its cause. Clinical ecologists are criticized for attributing their patients' illnesses to environmental factors when these patients clearly have other well-defined clinical diseases, such as depression. In some cases, these criticisms are justified. However, while ecologists are accused of over-zealously diagnosing environmental illness and overlooking other important medical conditions, some allergists have assumed that applying an accepted medical label to a patient's condition somehow rules out an environmental etiology. This is simply not the case. Indeed, both approaches are in error.

POSSIBLE MECHANISMS, DIAGNOSTIC APPROACHES, AND THERAPIES

Possible Mechanisms

It is apparent from the limited data available at this time that any mechanism or model that would purport to explain the syndrome of multiple chemical sensitivities would need to address the following features which seem to be associated with this illness:

1. Symptoms involving virtually any system in the body, or several systems simultaneously.

2. Differing symptoms and severity in different individuals, even those with the same exposure.

3. Induction (i.e., sensitization) by a wide range of environmental agents.

4. Subsequent triggering by levels of exposure that are often lower than those involved in initial induction of the illness.

5. Concomitant food intolerances, estimated to occur in a sizeable percentage of those with chemical sensitivities.

6. "Spreading" of sensitivity to other, often chemically dissimilar substances. Each substance may trigger a different constellation of symptoms.

7. Adaptation (masking), i.e., acclimatization to environmental incitants, both chemical and food, with continued exposure; loss of this tolerance with removal from the incitant(s); and augmented response with re-exposure after an appropriate interval (e.g., 4 to 7 days).

8. An apparent threshold effect referred to by some (including certain traditional allergists whom we interviewed) as the patient's "total load". Total load is a theoretical construct that has been invoked by clinical ecologists to help explain why an individual develops this syndrome at a particular time. Illness is said to occur when the total load of biological, chemical, physical and psychological stressors exceeds some threshold for the patient.

Although knowledge of the mechanism of a disease may be useful for developing better therapies, such knowledge is not a prerequisite for intervention. It may be possible to prevent the development of multiple chemical sensitivities in those not yet affected by controlling environmental exposures.

The most frequently cited theories to explain chemical sensitivity involve either the nervous system or the immune system or the interaction between them, since these two systems most clearly link the external environment and the internal milieu. The rapid responsiveness of these systems also makes them attractive candidates since symptoms of food or chemical sensitivity may develop within seconds of exposure. Other suggested mechanisms include damage to detoxification pathways and psychiatric causes.

The fact that some individuals have defective enzyme detoxification systems could help to explain why certain patients are more susceptible to foods and chemicals than others. Further, damage by a toxin might compromise detoxification pathways so that other substances formerly metabolized by this pathway can not be degraded properly, and thus might provoke symptoms at low exposure levels (a hypothetical basis for the spreading phenomenon).

Some psychiatrists are of the opinion that individuals with multiple chemical sensitivities suffer from atypical depression, hypochondriasis, post-traumatic stress disorder, hysteria, panic disorder, conversion disorder, or combinations of these. The symptoms of low-level chemical exposure may indeed include depression, difficulty concentrating, anxiety, peculiar bodily sensations, headaches, and other subjective symptoms. However, psychiatric disorders may be the result of the patient's illness, not the cause of it. Environmentally-induced disease is a testable hypothesis. It should be ruled out before a patient is labeled with a psychiatric diagnosis.

Diagnostic Approaches and Therapies

The majority of clinical ecologists use provocation-neutralization to a greater or lesser extent. This technique involves provoking a patient's symptoms by injecting or administering sublingually a small dose of an inhalant, food, or chemical while observing the patient for symptoms and/or increase in wheal size if given via a cutaneous route. This "diagnostic" test is used to identify incitants for a particular patient. Subsequently, various dilutions of the same substance that produced symptoms or a wheal are injected or given sublingually until one dilution is found that will "turn off" the patient's symptoms, or that results in no increase in wheal size following intradermal injection. This dose is called the "neutralizing dose".

There are many legitimate concerns regarding use of this technique for diagnostic and therapeutic purposes. The definitive study of provocation-neutralization has not yet been done. Nor have the studies purporting to prove its ineffectiveness been free from substantial flaws. Most convincing are individual cases in which symptoms appear dramatically with provocation. It may be that the technique works best in a select subgroup of patients. The collective strength of the dozen or so positive studies that have been done may be greater than that of any individual study; the statistical technique of meta-analysis may have relevance here as a tool for evaluating them further.

Too much emphasis has been placed upon trying to disprove the utility of this method for diagnostic or therapeutic purposes, as if the existence of the problem of multiple chemical sensitivities depended on provocation-neutralization. The existence of multiple chemical sensitivities and the efficacy of provocation-neutralization are independent issues and ought to be treated as such.

AREAS OF AGREEMENT AND DISAGREEMENT BETWEEN ALLERGISTS AND CLINICAL ECOLOGISTS

On the basis of interviews with key individuals in allergy, clinical ecology and occupational medicine, and on the basis of the literature we reviewed, we have discovered both areas of common ground regarding the chemically sensitive patient and areas of disagreement. While some observers allege that the tension between allergists and clinical ecologists stems from a competition for patients, there are fundamental differences in scientific/medical viewpoints. All physicians agree that chemical exposure can be harmful to any and all systems of the body. Disagreements exist as to what levels of exposure are necessary to cause health effects, what particular symptoms or diseases are associated with specific chemical exposures, and what mechanisms of causation come into play. There is a wide range of opinion as to the extent to which the problems of the chemically sensitive patient are psychiatric in origin.

Physicians agree that isolation of the patient in an appropriate environmental unit away from chemical substances in food, air and water is essential to unravelling the myriad substances that may be causing a variety of effects. More specifically, all of the traditional allergists with whom we spoke acknowledged that in the study or workup of patients with possible environmentally-induced disease, attention must be paid to the possible role of adaptation. Low-level exposure to chemicals must be avoided prior to testing patients for chemical sensitivities in order to avoid adaptation and the loss of a measurable effect.

Some allergists favor psychiatric referral for patients who do not improve, while clinical ecologists are of the opinion that the patients' problems, although difficult to solve, are nonetheless likely to be physical in nature. Ecologists feel that environmental factors must be carefully excluded (i.e., in a unit if necessary) prior to invoking psychiatric diagnoses.

All physicians agree there is a need for studies to clarify unproven therapies, and physicians in both allergy and clinical ecology agree that it would be best if they worked together to design the necessary protocols, conduct the studies, and evaluate the results. A few allergists are embracing the fundamentals of clinical ecology such as adaptation and avoidance, but hesitate to publicly identify their views with those of the clinical ecologists. Some allergists have been openly hostile to clinical ecology in the past. However, recently there has been a marked shift in the attitudes of some allergists and other specialists, who are tired of name calling and legal entanglement, which they recognize as contrary to their patients' best interests. Increasingly, they want to air and resolve their differences and identify avenues of cooperation.

THE ROLE OF MEDICAL PRACTITIONERS AND THEIR SOCIETIES

In this section we identify the potentially positive roles that primary care physicians, occupational/environmental health physicians, allergists, and clinical ecologists can play in addressing the needs of the chemically sensitive patient. The roles differ depending upon the group of patients in need. It would be fair to say that, at this time, patients consult clinical ecologists and allergists out of desperation, rather than as a result of referrals. It is our considered opinion that a structured, sensible referral strategy needs to be developed along the lines suggested in Table IX and discussed below.

Primary care physicians are in the best position to provide a knowledgeable referral for chemically sensitive patients--referring them to the health professional most likely to be of help to the patient. Workers exposed to industrial chemicals should be referred to occupational health clinics or occupational physicians. The coupling of industrial hygiene services and a detailed work history help occupational physicians decide what can be done for the chemically exposed patient. In the absence of or in cooperation with an occupational physician, an industrial hygienist may aid primary care physicians in identifying possible illness and relevant exposures.

Table IX
STRATEGIES FOR PRIMARY CARE PROVIDERS

Group	Strategies	
	Primary Referral	Subsequent Referral
Workers	Referral to Occupational Health Physicians* or Clinics* • Work histories • Industrial hygiene surveys	• Clinical ecologists* • Allergists* • Detoxification programs*
Occupants of Tight Buildings	Adults: As above for office workers Children: Clinical ecologists* or allergists*	As above for office workers
Contaminated Communities	With help of • State health department • EPA • ATSDR Referral to environmental/ occupational health physicians to take an environmental exposure history	• Clinical ecologists* • Allergists* • Detoxification programs*
Individuals		
Pesticides and other toxic substances	As for contaminated communities	As for contaminated communities
Indoor air (domestic)	• Clinical ecologists* • Allergists*	

* Selected with great care

If the problems that the worker is experiencing are those of classical toxicity, such as chronic lead poisoning, the occupational physician will be able to help the worker directly. In special cases, such as polybrominated biphenyls (PBB) exposure, some occupational physicians might refer the patient for detoxification therapy to remove the bio-accumulated toxins. When the worker is seen to exhibit chemical sensitivity of a non-traditional nature, the occupational physician may be able to help the patient himself if he is knowledgeable about multiple chemical sensitivity problems. Indeed, many occupational physicians are developing their knowledge in this emerging area. Alternatively, the occupational physician may refer the patient to either a clinical ecologist in whom he has confidence or to an allergist who is willing to investigate the possibility that the problem of multiple chemical sensitivities may be physical in origin.

Occupants of tight buildings, who could be suffering from either classical sensitivity, e.g. to molds, or from multiple chemical sensitivities, can also be referred to an occupational health clinic or an occupational physician. The occupational physician may then manage the patient him/herself or provide the appropriate referral, as described above.

For patients who comprise part of a contaminated community, the primary care physician should, ideally, involve the state health department and the Environmental Protection Agency (EPA) or the Agency for Toxic Substances and Disease Registries (ATSDR) which could document exposures and watch for a pattern of illness in that community. With the assistance of these agencies, the primary care physician can make appropriate referrals to physicians expert in occupational and/or academic environmental medicine. These physicians will take an environmental history in much the same manner an occupational physician takes a work history. This history needs to be coupled with disease patterns recognized by and with exposure measurements made by the state health and environmental protection departments, EPA or ATSDR. At that point the occupational or environmental medicine physician may make appropriate referrals to clinical ecologists or allergists in whom he has confidence. There are relatively few physicians who specialize in environmental medicine. Since environmental medicine and occupational medicine have similar knowledge bases and require many of the same skills, efforts should be directed at developing professionals who span both fields in order to better serve the chemically sensitive patient.

Finally, for the divergent group of individuals whose illness results from indoor air in the home, pesticide applications, or other chemical exposures, the primary care physician may need to find ways to identify those clinical ecologists and allergists who are able to help the chemically sensitive patient. This group of patients is most challenging because the patients are diverse and may not fit a particular pattern of illness like the patterns often seen in the workplace, in tight buildings, or as part of a contaminated community.

The strategies we have outlined for dealing with these four groups of patients need to be carefully developed and refined. The weakest link in affording the patient proper medical care involves raising the consciousness of primary care physicians or those specialists whom the patient might see in a random manner such as ear, nose

and throat specialists, neurologists, rheumatologists, and so forth. However, engaging the primary care physician is the first essential step in sending the patient down a directed pathway of proper referrals. The primary care physician's level of knowledge and concern regarding this problem must be given immediate attention.

The role of the medical specialty societies is central in facilitating the success of these referral strategies. For the primary care physicians, including those in family practice, internal medicine and pediatrics, a clear understanding of the problems of the chemically sensitive patient is requisite. For other specialists, their societies need to address the particular problems of chemical sensitivity that relate to their specialty.

The allergists need to adopt broader perspectives which several outstanding allergists seem to be doing. The allergy societies need to commit themselves to a critical but fair appraisal of those techniques and approaches that may be useful in expanding the practice of allergy beyond its present boundaries, e.g., use of an environmental care unit. Allergists need to be able to take comprehensive work and environmental histories, to learn about toxicity and chemical sensitivity, and to familiarize themselves with appropriate diagnostic and therapeutic approaches and techniques, for example, industrial hygiene evaluations of both the workplace and the home. Their societies should promote the practice of allergy with a broader vision. This can be done through continuing education efforts and by trying to build on common ground shared with clinical ecology and occupational medicine.

The clinical ecologists also need to learn to take better work and environmental histories, to be thorough in order to avoid overlooking other medical conditions, to engage in continuing educational activities in this rapidly developing area, and to put their work and techniques into a form that would serve as a useful primer for others. The environmental unit is an essential tool for both allergists and clinical ecologists and their knowledge should be combined in developing new units. The societies whose members practice clinical ecology need to develop rigorous standards for its practices.

RECOMMENDATIONS

Avenues for chemically sensitive patients must be established for obtaining information; appropriate medical referrals and, perhaps, related to this, access to an environmental unit; and medical insurance and disability compensation. Legal and social services are important.

Considering the needs of the chemically sensitive person and the community concerned with preventing an increase in the number of chemically affected individuals, we here turn to specific recommendations. Both state (New Jersey) and federal involvement is envisioned.

A. Research

(1a) The New Jersey Department of Health should establish a registry of chemically sensitive persons with the help of physicians, industrial hygienists, labor organizations, patient support groups and others. The purpose of the registry is to characterize the nature of the problem and trends over time, and to provide a basis for linkage to geographical information system analysis at some time in the future in order to discover sources of exposure.

(1b) The State of New Jersey should provide funding for a statistically useful questionnaire survey of these persons, stratifying respondents by group, e.g., occupationally exposed, occupants of tight buildings, members of contaminated communities, etc., and if possible, by the kind of exposure thought to be responsible for the person's condition, e.g., new carpeting, pesticides, etc.

(1c) The State of New Jersey should solicit the financial support of health insurance companies doing business in the state for this effort.

(1d) The New Jersey Department of Health should analyze the results of the survey in order to identify problem chemicals and affected groups that might serve as the focus for specific field studies.

(2) With the assistance of ATSDR, the New Jersey Department of Health should undertake field studies of various subgroups of chemically sensitized persons identified in (1d) above to document their illness. The groups should include occupational groups, contaminated communities, office workers and children. Studies should involve incidents where exposures have led to recognized problems, such as certain workplace exposures, toxic waste dumps and tight buildings.

(3) The New Jersey Department of Health should request the federal agencies, NIH, NIEHS, EPA and ATSDR, to construct a patient profile of those with chemical sensitivity by evaluating the Environmental Health Center in Dallas. Dr. William Rea has agreed in principle to such a study.

(4) The New Jersey Department of Health should press for a national conference to identify key areas for research into chemical sensitivity that might be undertaken by NIH, NIEHS, EPA, NIOSH and ATSDR. Allergists, immunologists, clinical ecologists and occupational/environmental physicians should participate as well as key governmental researchers.

(5) The New Jersey Department of Health should create an inter-agency working group of state agency professionals to guide the development of the state initiatives relevant to the problems of chemical sensitivity.

B. Information

(1) The New Jersey Department of Health should designate [a] professional[s] to staff a three-year effort addressing low-level exposures to chemicals. The designated professional (and necessary support staff) should be responsible for preparing written guidelines for the chemically sensitive person designed to assist the affected individual by providing him with a clear understanding of his condition and his options for diagnosis, treatment and compensation. The New Jersey Department of Health should provide a telephone "hot line" for the chemically sensitive person in order to guide his inquiries to the appropriate state agencies and offices.

(2) The New Jersey Department of Health should request the Robert Wood Johnson Medical Center to identify, compile, and maintain a list of physicians and clinics interested in handling the chemically sensitive patients with consideration, understanding and relevant medical or other interventions.

(3) The New Jersey Department of Health should prepare educational materials and hold short courses in conjunction with local medical associations giving guidance to primary care physicians in the recognition, diagnosis, treatment and referral options relevant to chemical sensitivity. Details of possible referral strategies were discussed in Section IX of this report.

(4) The New Jersey Department of Community Affairs, with the cooperation of the Departments of Health and Environmental Protection, should convene a meeting of those concerned with the design and construction of public and private office buildings to inform them of the problems of indoor air pollution.

C. Health Care

(1) The New Jersey Department of Health should seek state funds to enhance the capabilities of existing occupational health clinics to address problems of chemical sensitivity through financial and professional support.

(2) The New Jersey Department of Health should encourage the insurance carriers to provide industrial hygiene services for homes, and workplaces where multiple chemical sensitivities are suspected. Schools, where problems are indicated, should be investigated by the State.

(3) The New Jersey Department of Health should seek state funds to establish a pilot or demonstration environmental health unit at the Robert Wood Johnson Medical School, assisted by those experienced in establishing and operating a successful unit.

(4) The New Jersey Department of Health should encourage the Department of Education to evaluate the size of the problem among school children and to consider establishing [a] special classroom[s] for chemically sensitive children. These special classrooms should be used to study and document the impact of avoidance measures for this subpopulation.

D. Alternative Employment and Housing

(1) The State of New Jersey should educate employers about the chemically sensitive and encourage employers to provide alternative worksites within their places of employment, and in some cases, to allow employees to work at home while they improve. The state should also inform employers and employees of their obligations and rights under federal and state legislation for the handicapped.

(2) Vocational rehabilitation programs should be established for the chemically sensitive worker, coordinated with programs and activities of the State Department of Labor and Workers' Compensation Board.

(3) The working group established by recommendation A-5 above, should be convened to coordinate efforts related to alternative employment discussed above and to study housing needs. One option to be studied should be the establishment of "half way" houses where newly diagnosed persons or less severely affected persons can recover and receive guidance. Options for the establishment of experimental communities in less polluted environments should also be seriously investigated.

E. Medical Insurance

(1) The New Jersey Departments of Health and Insurance should undertake a study of economic savings that might result from timely and effective medical intervention for chemically sensitive persons.

The New Jersey Department of Health and Department of Insurance should use their good offices to express their disapproval of attempts to curb reimbursement for health care for chemically sensitive patients. This effort should be directed towards HCFA, Blue Cross/Blue Shield and other health insurance carriers. As the problems of the chemically sensitive become better understood, the state should do all within its power to facilitate recognition of chemical sensitivity for both health insurance and disability purposes.

F. Compensation

The New Jersey Department of Health should convene a meeting with the Department of Insurance and the New Jersey Workers' Compensation Board to explain the work-relatedness of chemical sensitivity.

G. Social and Legal Services

The working group created by recommendation A-5 should study the state's options for providing access to medically related social and legal services to persons whose illness stems from chemical sensitivity.

H. Regulation of Chemicals

The New Jersey Department of Health, in conjunction with the New Jersey Department of Environmental Protection and New Jersey Department of Labor, should consider revising or adding state standards to deal with low-level exposure to chemicals in the environment, industrial workplace and office and consumer products. New ventilation standards currently under consideration for public buildings is one example of desireable preventative measures. Just as "no smoking" areas are provided in public and private facilities, environmentally acceptable areas could be required. The state should work closely with the U.S. Environmental Protection Agency's Office of Indoor Air Pollution to establish federal policy for chemical sensitivity.

I. Resolution of Conflicts Among Medical Practitioners and their Societies

1. The New Jersey Department of Health should facilitate dialogue and an easing of antagonisms among allergists, clinical ecologists and occupational/ environmental physicians through educational efforts (see Recommendation B-3) and through co-sponsorship of conferences on chemical sensitivity (see Recommendation A-4).

PART ONE

I. INTRODUCTION

Chemical exposures are endemic to our modern industrial society. Patients who believe they are chemically sensitive are caught up in an acrimonious cross-fire among several different groups of physicians--traditional allergists; clinical ecologists; and in some cases, ear, nose and throat specialists, occupational physicians, and others. This acrimony is fueled by different medical paradigms of the definition, diagnosis, and treatment of disease or symptoms associated with exposure to low levels of chemicals in food and water, the outdoor environment, the work environment, indoor air, and consumer products. Legal conflicts further complicate the associated scientific and medical differences. Attempts by "chemically sensitive" persons to obtain workers' compensation, disability payments, and damage awards from employers and from the producers and users of chemical products result in an adversary system which draws medical practitioners unwillingly into the center of the conflict. Further exacerbating the situation are the insurance industry and employers who seek to reduce costs for medical care continuing the volatile history of economic tugs-of-war characteristic of health care in general. "Chemically sensitive" patients seek medical care and consideration from traditional medical practitioners, many of whom are ill-equipped or reluctant to provide the painstaking and time-consuming attention that is required for their condition.

This report was commissioned by the New Jersey Department of Health in order to clarify the nature of chemical sensitivity and to identify ways in which a state department of health can assist the chemically sensitive person and disengage the patient from the cross-fire described above and its attendant conflicts. In undertaking this task, we reviewed much of the available scientific and medical literature relating to low-level chemical exposure and resulting disease. We interviewed key individuals in various medical disciplines including allergy, clinical ecology, and occupational medicine. This was facilitated by the fortuitous scheduling of national conferences by the allergists and by the clinical ecologists in the same seven-day period in Texas in February of 1989. (See Appendix A for a list of persons interviewed.) Physicians involved with the chemically sensitive patient are concerned about being drawn into a legal and political struggle that ultimately may not help the patient. Through our interviews we were able to identify not only areas of conflict between the allergists and clinical ecologists, but also unexpected areas of common ground.

This report comes at a critical time. Since the Canadian Province of Ontario completed a report on "environmental hypersensitivity disorders" [Thomson 1985] in 1985, chemical sensitivity has received unprecedented attention from many quarters in the United States. A "Workshop on Health Risks from Exposure to Common Indoor Household Products in Allergic or Chemically Diseased Persons" was held by the National Academy of Sciences (NAS) on July 1, 1987 in which an 18-month study was recommended to address the "15 percent of the U.S. population [who] have an increased allergic sensitivity to chemicals commonly found in household products, such as detergents, solvents, pesticides, metals and rubber, thus placing them at increased risk [of] disease" [National Research Council 1987]. While that study has not yet been funded, in 1989 the NAS convened a panel to examine the interrelationships of toxic

exposures and immune response. Later the same year, the U.S. Office of Technology Assessment (OTA) began a study of non-cancer risks of chemicals, including immunotoxicity. Scheduled for 1990 is a Canadian Federal Advisory Committee on multiple chemical sensitivity.

The U.S. Congressional Research Service has issued a report on indoor air pollution in which chemical sensitivity is explicitly recognized [Courpas 1988, p. CRS-9]. The Environmental Protection Agency (EPA) acknowledges that health problems exist with low-level exposures well below those allowed by existing regulations [Claussen 1988] and in its Report to Congress on Indoor Air Quality, EPA identifies multiple chemical sensitivities as a health concern [EPA 1989, 16]. The Superfund Amendments, SARA, Title IV mandate a vigorous investigation of the problems of indoor air pollution by EPA. Professor John D. Spengler of Harvard University's School of Public Health, a leading authority on indoor air pollution, has testified:

> "There is growing evidence that there are chemically sensitive individuals in our society. Many, it is believed, may have acquired the sensitivity due to chronic exposures. But even without frank illness, the syndrome of irritation, fatigue, shortness of breath and nausea associated with building-related problems results in lost productivity and wasteful investigations and litigation." [Spengler 1988]

Legislation has been introduced in Congress [S.1629, H.R. 5373] that explicitly recognizes multiple chemical sensitivities as a serious threat to public health resulting from indoor air pollutants. The State of Maryland has completed a study of "chemical hypersensitivity syndrome" [Bascom 1989]. Legislation establishing a demonstration program to provide services and assistance to chemically hypersensitive persons [S.696] is likely to be introduced in New Jersey. These activities underscore a groundswell of activity that requires in-depth and thoughtful attention to chemical sensitivity.

We are at a critical crossroads. There is at this time a small window of opportunity which may be closed if we do not take action to address the problems of the chemically sensitive individual in a caring and equitable way. The recommendations made in this report result from our interviews, literature review, and examination of the issues, and we suggest that their adoption is necessary for making substantial progress in this area.

This report is divided into three parts. Part One includes this introduction (Section I) and discusses sensitive populations and low-level exposures to chemicals (Section II), and the history of clinical ecology and its relationship to other disciplines (Section III).

Part Two addresses the magnitude and nature of the problem (Section IV); possible mechanisms, diagnostic approaches and therapies (Section V); and a

summary of areas of agreement and disagreement between allergists and clinical ecologists (Section VI).

Part Three discusses research needs (Section VII); patient and community concerns; health care, insurance and compensation needs (Section VIII); and the role of medical practitioners and their societies (Section IX). Section X contains recommendations for the New Jersey Department of Health (NJDOH). While these recommendations are tailored specifically for the State of New Jersey, they also envision federal government involvement and have nation-wide applicability.

II. SENSITIVE POPULATIONS AND LOW-LEVEL EXPOSURES TO CHEMICALS

A. Groups Sensitive to Low-Level Chemical Exposure

A review of the literature on exposure to low levels of chemicals reveals four groups or clusters of people who may be chemically sensitive:

(1) Industrial workers

(2) Occupants of "tight buildings," including office workers and school children

(3) Residents of communities whose air or water is contaminated by chemicals

(4) Individuals who have had personal and unique exposures to various chemicals in domestic indoor air, pesticides, drugs, consumer products, etc.

These four groups are listed for comparison in Table I. Note that while they differ in professional and educational attainment, age and sex, and the mix and levels of chemicals to which they are exposed, all have multiple symptoms involving multiple organ systems with marked variability in type and degree of those symptoms. Symptoms are often "subjective." For example, central nervous system (CNS) symptoms such as difficulty concentrating or irritability are common and physical examinations are frequently unremarkable for individuals in each category. Careful analysis of these groups may reveal differences that can illuminate the etiologies and suggest effective therapeutic options for the myriad problems comprising chemical sensitivity. These differences also may create a referral or selection bias such that members of the four groups present themselves preferentially to different medical practitioners, e.g., some may consult occupational health physicians, others primary care physicians, and still others clinical ecologists or allergists. (See later discussion in Section VII on Research Needs.)

Problems experienced by people in tight buildings, and by industrial workers in a particular workplace or by the residents of a contaminated community occur within a relatively short time period--perhaps weeks or a few months. These problems may occur after a recognized event such as the installation of new carpeting, relocation to a new workplace, or changes in workplace or community exposures. The "temporal cohesiveness" of exposures and problems can contribute to the recognition of the problem as real. Acceptance of these problems as bona fide physical disease may also be facilitated by the recognition that these problems are widespread in nature and simply are not limited to what some observers would describe as malingering workers, hysterical housewives, and workers experiencing mass psychogenic illness. We are struck by the fact that individuals in such demographically divergent groups as those in Table I, ranging from industrial workers, to office

Table I
CHEMICALLY SENSITIVE GROUPS

	Nature of Exposure	Demographics
(1) Industrial Workers	Acute and chronic exposure to industrial chemicals	Primarily males; blue collar; 20 to 65 years old
(2) Tight Building Occupants	Off-gassing from construction materials, office equipment or supplies; tobacco smoke; inadequate ventilation	Females more than males; white collar office workers and professionals; 20 to 65 years old; school children
(3) Contaminated Communities	Toxic waste sites, aerial pesticide spraying, ground water contamination, air contamination by nearby industry and other community exposures	All ages, male and female; children or infants may be affected first or most; pregnant women with possible effects on fetuses; middle to lower class
(4) Individuals	Heterogeneous; indoor air (domestic), consumer products, drugs and pesticides	70-80% females; 50% in 30 to 50 year age bracket [Johnson 1989]; white, middle to upper middle class and professionals; farmers

workers, housewives, and children, report similar polysymptomatic complaints triggered by chemical exposures. Perhaps some common thread unites these individuals. The similarities in terms of both their medical complaints and exposure histories may be more than coincidental.

Part Two of this report explores the variety of offending substances and health effects associated with low-level exposures to chemicals. It also attempts to shed some light on possible mechanisms, diagnostic approaches and therapies of importance to the chemically sensitive patient. First, however, it is essential to address the question: what is chemical sensitivity?

B. Types of Sensitivity

The term "sensitivity" may have at least three different meanings, and this is at least partially responsible for the confusion surrounding chemical sensitivity.

Individuals differ in their response to increasing doses of a toxic substance. The underlying causes of inter-individual variability include age, sex, and genetic makeup; lifestyle and behavioral factors, including nutritional and dietary factors, alcohol, tobacco and drug use; environmental factors; and pre-existing disease [Ashford 1984]. In the classical, toxicological use of the word "sensitivity", those individuals who require relatively lower doses to induce a particular response are said to be more sensitive than those who would require relatively higher doses before experiencing the same response [Hattis 1987]. A hypothetical distribution of sensitivities, i.e., the minimum doses necessary to cause individuals in a population to exhibit a harmful effect is shown in Curve A in Figure 1. [If we plot the cumulative numbers of individuals who exhibit a particular response as a function of dose, we generate a population dose-response curve. (See Curve A in Figure 2.)] This distribution describes the traditional toxicological concept of sensitivity. Curve A in Figure 1 illustrates that health effects of classical diseases are seen in a significant portion of the normal population at a certain dose; the sensitive and resilient populations are found in the tails of the distribution. (Of course not all toxic substances have large variances or significant tails.) Painstaking scientific research and removing the effects of confounding have resulted in the discovery of sensitive individuals at levels heretofore considered safe. Recent work on lead [Bellinger 1987] and benzene [Rinsky 1987] are but two examples. For the sensitive person, avoidance of low-level exposures should generally lead to improvement, or at least lead to the arrest of the development of the disease.

A second meaning of the word "sensitivity" appears in the context of classical IgE-mediated allergy (atopy). Here, the atopic individual exhibits a reaction, while non-allergic persons do not, even at the highest doses normally found in the environment. A hypothetical sensitivity distribution for an atopic effect is shown in curve B of Figure 1., and the dose-response curve derived from that distribution is found in curve B of Figure 2.

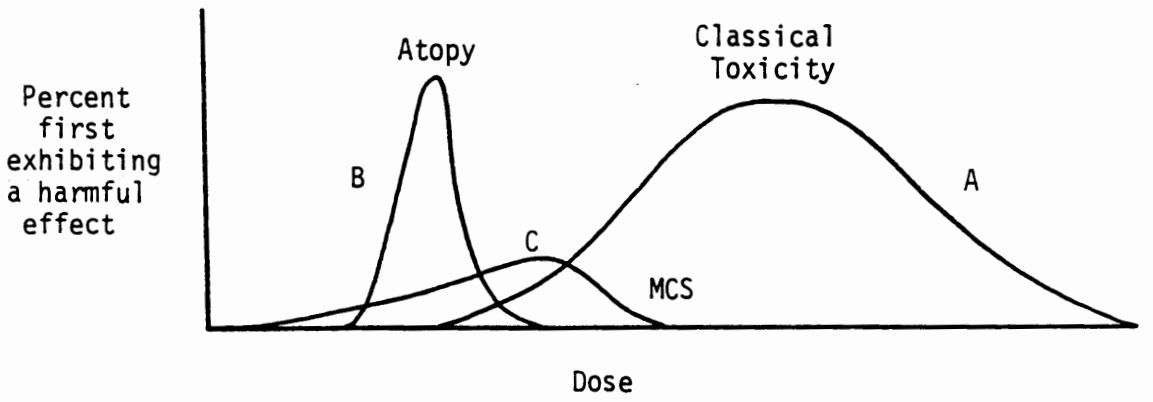

Figure 1: Distribution of Different Types of Sensitivities as a Function of Dose

Curve A is a hypothetical sensitivity distribution for classical toxicity, e.g., to lead or a solvent. "Sensitive" individuals are found in the left-hand tail of the distribution.

Curve B is a hypothetical sensitivity distribution of atopic or allergic individuals in the population who are "sensitive" to an allergen, e.g., ragweed or bee venom.

Curve C is a hypothetical sensitivity distribution for individuals with multiple chemical sensitivities who become "sensitive" to particular incitants, e.g., formaldehyde or phenol.

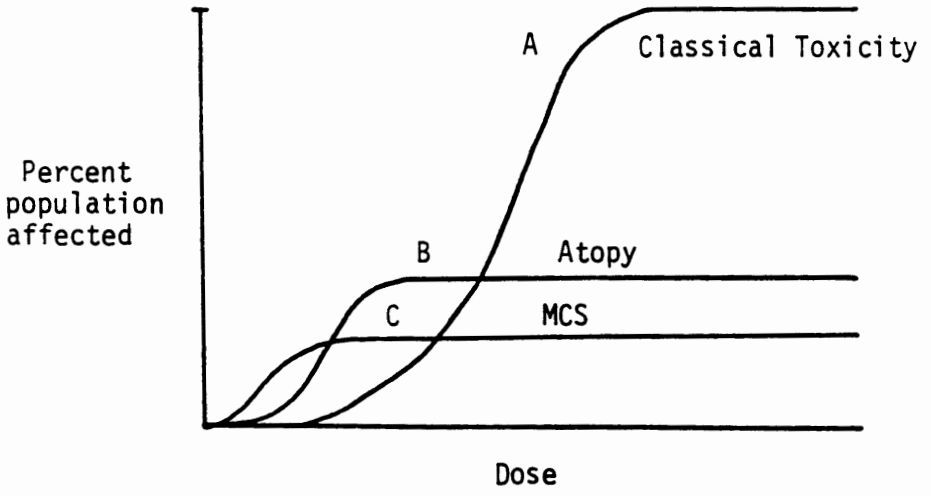

Figure 2: Population Dose-Response Curves for Different Effects

Curve A is a hypothetical cumulative dose-response curve for classical toxicity, e.g., to lead or a solvent. "Sensitive" individuals are found in the left-hand tail of the curve.

Curve B is a hypothetical cumulative dose-response curve for atopic or allergic individuals in the population who are "sensitive" to an allergen, e.g., ragweed or bee venom.

Curve C is a hypothetical cumulative dose-response curve for individuals with multiple chemical sensitivities who become "sensitive" to particular incitants, e.g., formaldehyde or phenol.

Patients suffering from multiple chemical sensitivities may be exhibiting a third and entirely different type of sensitivity from those described above. Their health problems often (but perhaps not always) appear to originate with some acute or traumatic exposure, after which the triggering of symptoms and observed sensitivities occur at very low levels of chemical exposure. The inducing chemical or substance may or may not be the same as the substances that thereafter provoke or "trigger" responses. (Sometimes the inducing substance is described as "sensitizing" the individual, and the affected person as a "sensitized" person.) Reactions may sometimes be observed at incitant levels similar to those to which classically sensitive and atopic patients respond. However, unlike classical toxicity, here the effects of low-level exposures are not simply those effects observed in normal populations at higher doses. The fact that normal persons, e.g., most doctors, do not experience even at higher levels of exposure those symptoms that chemically sensitive patients allege they have at much lower levels of exposure probably helps to explain the reluctance of some physicians to believe the problems are physical in nature. (While this also describes atopy, here the sensitivity is not IgE mediated.) To compound the problem of physician acceptance of this illness, multiple organ systems may be affected and multiple substances may trigger the effects. Over time, there seems to be a spreading of sensitivities, both in terms of the types of triggering substances and the systems affected [Randolph 1962, 98 and 119]. Avoidance of the offending substances is usually effective, but much more difficult to achieve for these patients than for classically sensitive patients, since the problems may occur at extremely low doses and the exposures are ubiquitous. Adaptation to chronic low-level exposure with consequent "masking" of symptoms (discussed more fully below) may make it exceedingly difficult to discover these sensitivities and unravel the multifactorial triggering of symptoms. A hypothetical sensitivity distribution for a single symptom for the already chemically sensitive person in response to a single substance trigger is shown in curve C of Figure 1 and the corresponding dose-response curve is shown in curve C of Figure 2.

It is conceivable that exposure to certain substances, such as formaldehyde, might elicit all three types of sensitivities.

The fact that sensitivity means something quite different to toxicologists, allergists, and clinical ecologists reflects the different disease paradigms under which each operates. Neither traditional allergists nor toxicologists fully appreciate the two-step process, induction and triggering, that seems to characterize multiple chemical sensitivities.

Those clinical ecologists who reference the literature on classical chemical toxicity to buttress their case for chemical sensitivity may be adding to the confusion and may be contributing to the reluctance of others to accept their ideas. Likewise, allergists who dismiss chemical sensitivity on the grounds that it is not consistent with the IgE-mediated sensitivity they know best may be overlooking another kind of sensitivity in their patients. While chemicals may act in some manner to predispose or cause the body to be reactive to subsequent low-level chemical exposures, this latter effect, i.e., hyper-reactivity to low levels of chemically diverse and unrelated

substances, is not toxicity as classically defined or understood at this time. (See Section V for a fuller discussion.)

Physicians who see more or less random individuals who are not members of an identifiable exposure group are less likely to recognize patterns or similarities among these patients who claim to be chemically sensitive. Now that more attention is being focused on problems of industrial workers, occupants of tight buildings, and families in contaminated communities, these "random" patients (the fourth group in Table I) may be diagnosed more readily. Once physicians recognize a constellation of symptoms that occur repeatedly in individuals who share similar exposure histories, the "disease" seems to change its label from "idiopathic" or "psychogenic" to a recognized disorder, such as has occurred in the case of sick building syndrome [Kreiss 1989]. Cullen's recent book on multiple chemical sensitivities was stimulated by his observations of a particular pattern of symptoms among workers heretofore unfamiliar to most occupational physicians [Cullen 1987]. In the future, patterns observed in occupational and other groups of patients should facilitate a better understanding of what seems to many to be a hopeless confusion of symptoms reported by patients.

III. CHANGES IN CHEMICAL PRODUCTION/USE AND THE EMERGENCE OF CLINICAL ECOLOGY

In the conclusion to his book, Workers with Multiple Chemical Sensitivities, Cullen writes:

> "The health problems of workers who react to low levels of environmental pollutants and chemicals, increasingly reported and recognized in recent years, has [sic] posed a serious dilemma for health providers from a wide array of disciplines, including generalists, internists, family practitioners, allergists, psychiatrists, social workers, and frequently occupational physicians and nurses. The inability of these professionals to provide satisfactory care from the patient's perspective has led to the emergence of new and alternative clinical theories and approaches, challenging traditional views. Unfortunately, the success of these alternative approaches has also not been demonstrated, fueling an ever widening and hostile debate in which the patient is held hostage and virtually all clinicians are rendered impotent because of widely known intraprofessional disagreements. [Cullen 1987b, 804, emphasis added]

How did these disagreements arise? And why are more and more problems related to low-level exposure to chemicals being reported in recent years? Is there merely increased recognition of the problem or an actual increase in numbers of individuals being affected? We shall try to shed some light on these questions by examining the development of this problem and changes in chemical production, consumer products, and building design that have accompanied its emergence. We also include a brief history of clinical ecology, noting its split from allergy, and its subsequent growth and continued conflicts with traditional allergists.

The increased medical interest in exposure to chemicals, especially low-level exposures, accompanied changes in the production of synthetic organic chemicals, building construction and indoor air quality. With the concern for energy conservation in the 1970's, homes and office buildings in the United States were constructed more tightly and make-up air (fresh air intake) was cut to a minimum. The historical trend of ventilation standards, used by architects and building designers, can be seen in Figure 3 [Mage]. The earliest standard, proposed by Tredgold in 1824 to prevent stuffiness, provided four cubic feet per minute (cfm) fresh make-up air per occupant. In 1893 Billings recommended 30 cfm per person, a value that subsequently was adopted by the American Society of Heating and Ventilation Engineers (ASHVE) and incorporated into the building codes of twenty-two states by 1925. In 1936 this was lowered to 10 cfm per person in response to research by Yaglou on the threshold of detection for human body odors; the American Standards Association adopted this value in 1946. Thus, before the energy crisis of 1973-1974 odor detection was the basis for the ventilation standard. But in 1973, because of energy concerns, ASHRAE (American Society of Heating, Refrigeration and Air Conditioning Engineers) lowered the standard to 5 cfm, and forty-five states adopted this into their codes. The 5 cfm

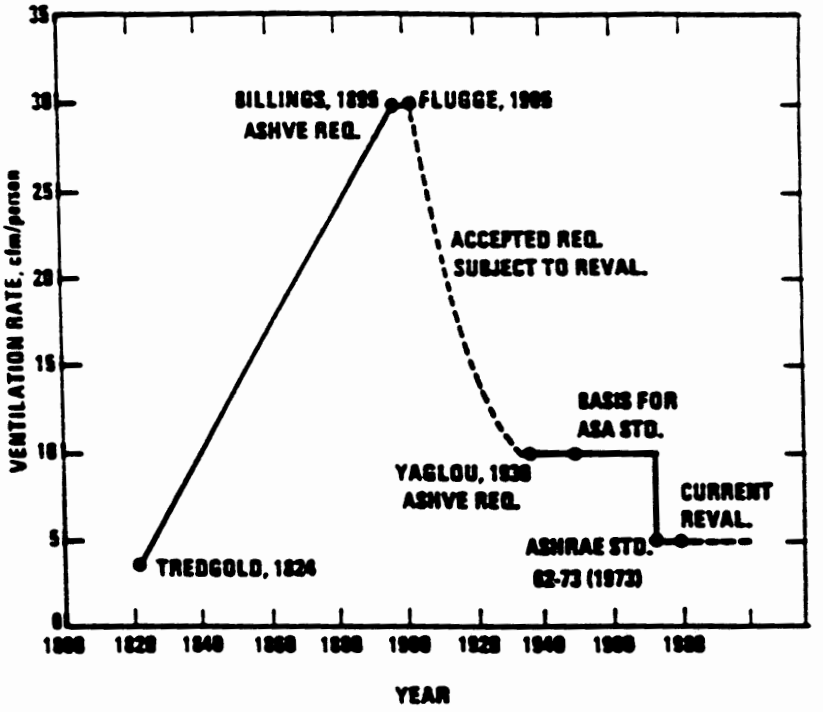

Figure 3: Historical Development of Ventilation Standards in the United States

Source: Mage 1985

Reprinted with permission from Mage, D. and R. Gammage, "Evaluation of Changes in Outdoor Air Quality Occurring Over the Past Several Decades," in Indoor Air and Human Health, R. Gammage and S. Kaye, Eds. (copyright 1985, Lewis Publishers, Inc., Chelsea, MI).

standard did not take into account the increased use of off-gassing synthetic materials indoors and their possible health consequences. Currently, ASHRAE is considering revision of the standard [Massachusetts 1989, 38].

Similarly, homeowners and new home builders caulked and sealed, installed storm windows and extra insulation, effectively reducing fresh air infiltration. Such repairs were economically advantageous and in part tax-deductible. In older homes (not given these energy overhauls) the average fresh air infiltration rate is almost twice that of newer homes (0.9 versus 0.5 air changes per hour), but individual homes vary tremendously from 0.1 to more than 3 air changes per hour [Mage 1985]. See Figure 4.

Over 800 different volatile compounds were observed inside four buildings studied by the EPA [Wallace 1985]. Wallace summarizes recent studies of indoor air pollutants:

> "1. Indoor median concentrations of volatile organics are consistently greater, by factors of 2 to 5, than outdoor medians.
>
> 2. At higher concentrations, the indoor-outdoor ratio increases, often beyond factors of 10.
>
> 3. Concentrations are extremely variable, covering 3 to 4 orders of magnitude, indicating the presence of intense indoor sources.
>
> 4. These sources are many, including paints, adhesives, cleansers, cosmetics, and other consumer products and building materials; but also [include] common activities, such as visiting the dry cleaner shop or even taking a hot shower!" [Wallace 1985]

Remarkably, these sources are the same ones individuals with multiple chemical sensitivities identify as provoking their vague and seemingly inexplicable symptoms. With their homes and workplaces already filled with synthetic materials that off-gas, gas furnaces, cigarette smoke and other sources of pollutants, Americans sealed their buildings for energy efficiency. Not surprisingly, indoor air pollution levels rose dramatically and so did health complaints. In addition, Americans were spending many more hours per day indoors, at work and at home, in schools, shopping malls, etc., than preceding generations [Environmental Protection Agency 1989; Massachusetts 1989].

With indoor air pollution on the rise since World War II, and now tighter, more energy-efficient construction of schools and workplaces, outbreaks of sick building syndrome appeared in the late 1970s. Chlorine production is felt by some to provide a useful index of the increased quantities of synthetic organics that are found indoors (e.g., polyvinyl chloride). Figure 5 [Mage 1985] shows the dramatic rise in chlorine production in billions of pounds per year that has occurred since World War II, plotted against mean sperm density, a widely recognized and subtle indicator of the

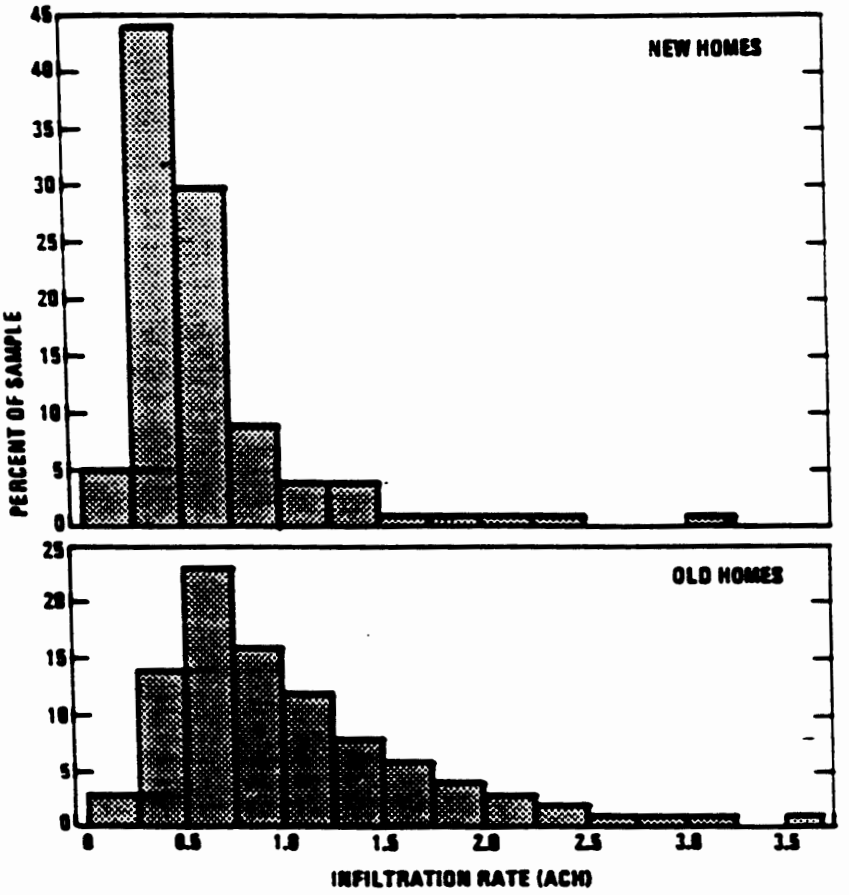

Figure 4: Infiltration Rates in U. S. Houses
Air Changes per Hour (ACH)

Source: Mage 1985

toxic effects of a variety of chemicals, e.g, lead. Actually, increases in chlorine production underestimate increases in the amount of synthetic organics. Before World War II, U. S. production of synthetic organic chemicals totalled fewer than one billion pounds per year. By 1976, production had soared to 163 billion pounds annually [Odell 1980, 213]. Increased sources of indoor air pollution, coupled with decreased fresh make-up air, have transformed the indoor environment. Community exposures to toxic chemicals, industrial and office exposures, and other episodic exposures of individuals also increased, reflecting the rise in production of coal and oil derived chemicals and synthetics.

These changes in chemical production, consumer products, and building design have been accompanied by an increasing number of people who appear to react to low levels of environmental pollutants. Indeed, since World War II there seem to have been upsurges in certain illnesses, e.g., asthma [Sly 1988] and depression [Klerman 1989]. Many patients, frustrated by their lack of success with traditional medicine, have sought the care of clinical ecologists.

Theron Randolph and a number of other clinical ecologists are board-certified allergists. Randolph received his M.D. degree from the University of Michigan, where he completed his residency in Internal Medicine. His allergy/immunology fellowship was done at Massachusetts General Hospital and Harvard Medical School in 1942-1944. He entered private practice in Chicago where he also served as a clinical instructor in Allergy at Northwestern University Medical School for several years. Randolph reported that many of his patients reacted adversely to commonly eaten foods such as corn (a food that is ubiquitous in the American diet in the form of sugar, starch, and oil, as well as in its unrefined state), wheat, milk, and eggs. Indeed, he later described corn allergy as "the most common food allergy in North America" [Randolph 1980, 109]. He used Rinkel's technique [Rinkel 1944, 1951] of having patients avoid specific foods for four to six days (and not much longer) prior to test feeding them to "unmask" such reactions. It was Herbert Rinkel, another American allergist, who first described the phenomenon of "masking" and its clinical application for food sensitivities.

According to ecologists, most allergists then, as now, do not recognize or employ this avoidance or "unmasking" period prior to testing and thus never see this type of food sensitivity in their patients. Recent guidelines on food testing written for allergists and published in their journal do not address this issue [Bock 1988]. Many traditional allergists recognize primarily IgE-mediated, immediate reactions to foods which generally are more readily observable by the investigator and do not require an avoidance period in order to detect them.

In 1951, Randolph realized that not only foods, but also chemicals, might be responsible for some of his patients' symptoms. A physician's wife who sold cosmetics had been seeing Randolph over a four-year period for rhinitis, asthma, headache, fatigue, irritability, depression, markedly fluctuating weight and intermittent episodic loss of consciousness [Randolph 1987, 73-76]. At each visit, he recorded almost verbatim on his typewriter the patient's statements about her condition, without

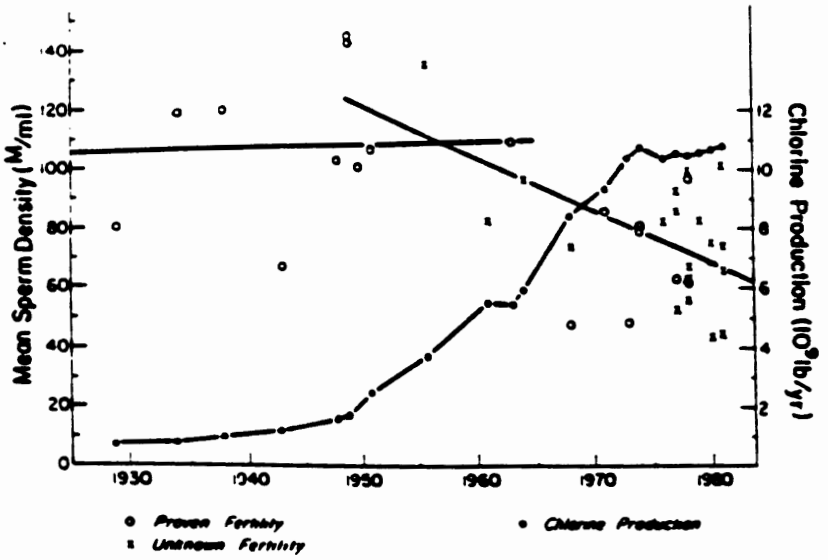

Figure 5: Increasing Chlorine Production in the U.S. and the Apparent Reduction in Human Sperm Density

Source: Mage 1985

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editing. By 1951, he had compiled 50 single-spaced typewritten pages concerning this woman. Reading over these pages, he realized there was a common denominator--each event was associated with exposure to gas, oil, coal, or their combustion products. Similar observations in other patients followed. A few years later, in 1954, Randolph published a series of six abstracts in the Journal of Laboratory and Clinical Medicine concerning "allergic type" reactions to industrial solvents and liquid fuels, mosquito abatement fogs and mists, motor exhausts, indoor utility gas and oil fumes, and chemical (coal or petrochemically derived) additives in foods, drugs and cosmetics [Randolph 1954a-f].

Randolph and other ecologists often refer to chemical sensitivities as the "petrochemical problem," since the increase in the incidence of this illness seems to parallel the growth of the petrochemical industry and the increased use of synthetic materials such as particle board, pesticides, synthetic textiles, plastics, and food additives by consumers since World War II. Late in the 1950's, Randolph adopted the term "clinical ecology" in order to describe his practice and its focus on environmental incitants and in order to avoid use of the word "allergy".

Randolph, who had been hospitalizing patients and testing them for their food sensitivities, found that another critical element in many of his patients' recoveries was avoidance of environmental chemical exposures in their jobs and/or homes while in the hospital. He developed a diagnostic approach termed "Comprehensive Environmental Control," in which patients avoid exposures to synthetic chemicals in order to facilitate diagnosis of chemical sensitivity. The next section describes this method in detail.

Although Randolph reported treating a wide range of illnesses successfully, his and other clinical ecologists' enthusiasm for this approach was not shared by many of their contemporaries. Randolph's early work showing that environmental influences can provoke mental and behavioral disturbances in a demonstrable, cause-and-effect way occurred in the 1950's, at the same time modern psychopharmacology was developing and the use of phenothiazine tranquilizers was expanding. Drugs that could control behavior, so-called "chemical restraints," were easy to administer and mass-applicable, and drug companies promoted them widely. University research in psychiatry, funded by drug companies, became focused on the development of better drugs. Only later were the long-range complications of many of these drugs realized. The dominance of psychoanalytical, behavioral, and pharmacological approaches to mental illness abrogated any major attempts by psychiatrists to look for food or chemical triggers for their patients' illnesses [Randolph 1987, 188]. Randolph and other clinical ecologists are critical of these developments in psychiatry: "...especially psychoanalysis, despite its wide application, has been devoid of any demonstrable evidence of etiology and has been relatively ineffective therapeutically" [Randolph 1987, 190-191].

As clinical ecologists continued to apply their concepts of environmental illness, many of which did not appear dependent upon immune mechanisms, they distanced themselves more and more from traditional allergists. In 1906 von Pirquet

coined the name "allergy" and defined it as "altered reactivity" of whatever origin. Thus the word "allergy" as originally used embraced both immunity and hypersensitivity [Corwin 1985]. In 1925 European allergists influenced their American colleagues to redefine allergy in the context of antibodies and antigens. Randolph, Coca, and other allergists objected, preferring to call this development the "Immunologic Theory of Allergy," but the new definition of allergy prevailed. Thus clinical ecology, which was concerned with heightened reactivity of unknown etiology, did not fit under this new definition. In 1967 when IgE was discovered, it enhanced allergy's credibility as a specialty. (At the time, allergy shots were dimly viewed, even called "witchcraft" or "voodoo medicine" by some medical practitioners.) This provided allergists with a scientific basis for their practice and some began to look down on areas that did not have such a basis, e.g., clinical ecology. Thus the observations of clinical ecologists, irrespective of their validity or clinical utility, were excluded from allergy, in part because IgE did not appear to be involved. Allergy and clinical ecology have continued to develop and define their separate paradigms. In Tables IIA and IIB we present the salient differences in approach and philosophy.

These dueling paradigms have continued to hamper meaningful dialogue between the two groups. Clinical ecologists are not found in allergy departments in medical schools. Their articles seldom appear in premier allergy journals--many times, but not always, because the articles fall short of recognized standards for scientific publications. In the United States clinical ecologists are absent from academic medicine. In contrast, the Robens Institute, University of Surrey, England, has given ecologist William Rea a chair in Environmental Medicine. An Environmental Unit has recently been established at the Beijing Union Medical School in China. In Ontario, Canada, the Ministry of Health is funding a $600,000 study of food sensitivities at the University of Toronto as a result of the Ontario study on chemical hypersensitivity.

Feeling shut out of allergy, Randolph and several other allergists founded the Society for Clinical Ecology in 1965 and opened its doors to family physicians, otolaryngologists, ant other physicians interested or involved in the area. In 1984, the Society changed its name to the American Academy of Environmental Medicine, much to the chagrin of allergists, toxicologists, and other academicians in environmental medicine. Membership in the Academy has grown by 225 members in the last two years and presently totals 570 [Howard 1989].

Allergists continue to point to the scientific basis of their practice and their detailed knowledge of immune mechanisms. Clinical ecologists stress the importance of their clinical observations. To some degree, their conflicts are an extension of the traditional tension between academicians and clinicians--a tension that has served neither side well.

Unfortunately, these conflicts may result in adverse economic consequences for patients who are already frustrated by their illness and attempts to gain help. Allergists successfully persuaded Medicare not to reimburse for provocation-neutralization therapies for food allergies and they are often asked to provide

Table IIA
CONTRAST BETWEEN PARADIGMS OF TRADITIONAL MEDICINE AND ECOLOGICALLY-ORIENTED MEDICINE

	Traditional Medicine*	Clinical Ecology
Focus/Approach	Body-centered; diagnosis contingent upon laboratory or clinical findings; symptoms alone generally insufficient for diagnosis	Environmentally-oriented; diagnosis based upon temporal relationship between symptoms and chemical/food exposure; testing by avoidance and reexposure, sublingual or cutaneous provocation.
Stage at Which Disease is Diagnosed	End-organ damage generally must be present	Diagnosis may be made prior to end-organ damage, i.e., in a subclinical or pre-morbid state
View of Patient	Focus on bodily parts and their malfunction. The patient is sick.	Focus on patient's chemical exposures and diet habits. The patient's environment is sick.
Specialization	Anatomically demarcated**	No specialties per se. Concept of specialties considered limiting since environmental exposure may provoke symptoms in several systems simultaneously.
History-Taking	Review of all body systems by more thorough primary care-takers; organ-oriented by specialists. Limited emphasis on dietary factors except in certain diseases, e.g., obesity, diabetes, hypercholesterolemia. Minimal attention to environmental exposures (except smoking) unless issue raised by patient	The more thorough practitioners review symptoms involving each system and search for environmental contributors to patient's illness
Therapies	Drugs, surgery	Avoidance of environmental and food incitants; "neutralization" of symptoms by giving small dose of incitants; nutritional supplements; "detoxification"

* Within traditional medicine, allergists are among the practitioners who are most skilled in exploring environmental factors relating to a patient's illness. They also appreciate multiple organ involvement. Differences between allergy and clinical ecology are summarized in Table IIB.

** Patients become "trained" to limit their complaints to the specialist's organ of interest; thus they may not complain of a headache to their gynecologist or of a rash to their psychiatrist.

Table IIB
CONTRAST BETWEEN TRADITIONAL ALLERGY AND CLINICAL ECOLOGY

	Traditional Allergy*	Clinical Ecology*
Focus	Search for environmental triggers for symptoms/disease	Same as allergists
Practice Priorities (in terms of frequency of diagnosis/relative importance in their patient population)	1. Biological inhalants, e.g., pollen, dust mite, molds, etc. 2. Food sensitivities 3. Chemical incitants	1. Chemical incitants 2. Food sensitivities 3. Biological inhalants
Diagnostic Approaches:		
Biological Inhalants	Skin tests using extracts of pollens, molds, etc. Sometimes in vitro testing.	Skin testing also but using techniques/extract concentrations that differ from allergists.
Foods	Skin tests using food extracts or in vitro tests, but usually limited to IgE-mediated diseases, such as eczema. Some practitioners do use elimination diets and food challenges for diagnosis. Double-blind, placebo-controlled challenges preferred.	Elimination diet with removal of suspect foods (or fasting) for 4-7 days followed by feeding challenges; sublingual or cutaneous provocation-neutralization heavily relied upon by majority.
Chemicals	Interest in patient's chemical exposures includes occupational asthma, chemical "irritants" that exacerbate asthma and contact dermatitis. Also drug allergies or adverse reactions to drugs. "Chemical testing" limited to: 1. Skin testing for drugs (especially penicillin) 2. Patch testing for contact dermatitis 3. Inhalation challenges in specially constructed exposure chambers by a few practitioners (usually related to disability cases)	Low-level, often subtle chemical exposures (e.g., gas heat, formaldehyde, off-gassing from particle board) responsible for many diverse symptoms/diseases. Patient avoids incitants. Some practitioners use sublingual or cutaneous doses of certain chemicals to provoke and neutralize symptoms. A few practitioners perform inhalation challenges.
Therapies used	Avoidance where practical. Antihistamines, topical and systemic steroids, theophylline, inhaled cromolyn, etc. Immunotherapy.	Chemical, food incitants avoided to regain tolerance. Drugs generally are avoided because of potential to sensitize. Some use of pancreatic enzymes, oral cromolyn, transfer factor, nystatin for Candida (yeast) sensitivity, etc. "Neutralization" used by most. Rotary/elimination diets often using organically grown foods. Detoxification using saunas.
Definition of Allergy	Adverse reaction involving antigen-antibody or sensitized lymphocytes.	Adverse reaction to a substance.
View of Multiple ChemicalSensitivities	Varies greatly but majority of patients felt to have psychiatric disorders.	Consequence of exceeding patient's capacity to adapt to total environmental load.

* Practice styles vary widely and even overlap within these groups, e.g., some allergists treat for Candida hypersensitivity while some ecologists use traditional skin testing methods and immunotherapy for inhalant allergies.

independent assessments to insurance carriers who are contesting workers's compensation claims for disability associated with chemical exposure. One prominent allergist we interviewed was distressed at finding himself "on the wrong side" from the patient's perspective as a result of taking referrals from insurance carriers.

While conflicts and antagonisms continue to be played out between allergists and clinical ecologists, the fields of toxicology and epidemiology are expanding their recognition that chemicals are harmful at lower and lower levels [Ashford 1987].

Both classical toxicology and epidemiology have been invaluable in studies involving a single cause resulting in a single effect. With synergism (multiplicative effects of several toxins) or multiple effects, scientific investigations are more difficult to conduct and interpret. Indeed, one must take great care in the design of epidemiological studies for the discovery of chemical sensitivity. Since such a variety of inducing substances, and, subsequently, triggering substances, seems to be involved, several mechanisms could be operating simultaneously and the "disease" may not be the same in all cases. Performing retrospective epidemiological studies on chemically sensitive persons without carefully defining the group to be investigated may result in a dilution of the prevalence of significant health effects. On the other hand, stratifying groups too narrowly may not yield statistically significant findings.

At present, the allergists do not identify with the clinical ecologists, even though the ecologists are concerned with "altered reactivity." The toxicologists and epidemiologists do not seek to establish communication with the ecologists, even though the ecologists share their concern about exposure to toxic substances. If the model employed by clinical ecologists offers any insight into a cause-and-effect relationship between environmental incitants and illness, its application will be seriously hampered given the present state of affairs. Randolph has called for strengthening the relationship between toxicology and clinical ecology. We believe that some tenets of clinical ecology at its best will contribute to a dynamic toxicology, i.e., observing the effects of chemical incitants in real time as those effects evolve.

PART TWO

IV. MAGNITUDE AND NATURE OF THE PROBLEM

Chemical sensitivity presents a challenging puzzle for the scientist, physician, and public policy decision-maker. The pieces of the puzzle include (1) observations of possible offending or triggering substances and health effects, and (2) plausible mechanisms, diagnostic approaches, and therapies. While a definitive and accurate picture is yet to come, at this time the pieces--viewed collectively--provide sufficient evidence to conclude that chemical sensitivity does exist as a serious health and environmental problem and that public and private sector action is warranted at both the state and federal levels [see also Massachusetts 1989, 1]. Just how large a problem exists is not known at this time. The National Academy of Sciences has suggested, without providing documentation, that approximately 15% of the population may experience "increased allergic sensitivity" to chemicals [National Research Council 1987]. The existing evidence does suggest that chemical sensitivity is increasing and could become a large problem with significant economic consequences related to the disablement of productive members of society.

Part Two of the report considers observations of offending substances and possible health effects, and plausible medical/scientific theories concerning low-level exposures to chemicals. This review does not constitute a "proof" of multiple chemical sensitivity, but in our view it is highly suggestive of its existence and it does cast serious doubts on the detractions offered by many critics.

A. Terminology and Key Concepts

1. Terminology

A wide array of names has been applied to the syndromes suffered by patients with heightened chemical reactivity (see Table III). Each name has specific implications regarding the underlying cause, mechanism, or manifestations of the disease, and there is overlap. A major hindrance in achieving scientific respectability has been the difficulty in agreeing upon a definition for this condition (or conditions). Cullen has emphasized the importance of establishing a uniform case definition before meaningful epidemiologic studies can be undertaken [Cullen 1987b]. Cullen cautions, "however constructed, the goal of descriptive studies must be refinement of the diagnostic criteria, in particular the very tentative boundaries with other diagnostic entities such as allergic, anxiety, panic and post-traumatic stress disorders, and physiologic sequelae of central nervous system (CNS) intoxication or injury, especially by organic solvents." He acknowledges that there may be some overlap between these entities, and offers the following case definition:

> "Multiple chemical sensitivities (MCS) is an acquired disorder characterized by recurrent symptoms, referable to multiple organ

Table III

ATTRIBUTES OF NAMES FOR HEIGHTENED CHEMICAL REACTIVITY

Cause	Mechanism	Effect
Chemically-Induced (or -Acquired) Hypersusceptibility Chemically Acquired Immune Deficiency Syndrome		
Environmentally-Induced Illness	Immunologic Illness	Multiple Chemical Sensitivities
	Immunotoxicity	Multiple Chemical Sensitivity Syndrome
	Immune Dysfunction	Chemical Hypersensitivity Syndrome
	Immune Dysregulation	Universal Allergy
	Conditioned Odor Response	20th Century Illness
	Fear/Anxiety	Total Allergy Syndrome
	Mass Psychogenic Illness	Environmental Allergy
	Various Psychiatric Disorders	Cerebral Allergy
		Environmental Maladaptation Syndrome
		Food and Chemical Sensitivity

> systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms." [Cullen 1987a]

This case definition, intended for epidemiologic use, is intentionally narrow. Cullen excludes persons who react to substances no one else is aware of on the basis that such individuals may be delusional and excludes persons who have bronchospasm, vasospasm, seizures or "any other reversible lesion" that can be identified and specifically treated. Clinical ecologists, however, would argue that persons with bronchospasm, vasospasm, seizures and other illnesses excluded by Cullen may well have the chemical sensitivity problem. Each issue of the clinical ecologists' journal, Clinical Ecology, contains the following definition:

> "Ecologic illness is a chronic multi-system disorder, usually poly-symptomatic, caused by adverse reactions to environmental incitants, modified by individual susceptibility and specific adaptation. The incitants are present in air, water, food, drugs and our habitat."

Although the patients whom the clinical ecologists and Cullen see are demographically divergent, the definitions of their illnesses are remarkably alike. Both describe the chemically sensitive patient in similar terms. (See Section II of this report for a discussion of sensitive populations.) However, what is sorely needed is an objective test that can be applied in each individual case to determine, incontrovertibly, whether a particular person has multiple chemical sensitivities.

Given the multitude of environmental exposures (both chemical and food) which allegedly can result in a seemingly endless array of physical and mental syndromes and the frequent absence of findings on routine physical examination, the practitioner who sees these patients with their divergent and unfamiliar litany of complaints is at great disadvantage in trying to diagnose the condition.

To circumvent this problem, we propose the following operational definition of multiple chemical sensitivity, a definition that is based upon environmental testing:

> The patient with multiple chemical sensitivities can be discovered by removal from the suspected offending agents and by re-challenge, after an appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge.

For research puroses, challenges should be performed in a double-blind placebo-controlled manner. This definition embodies the approach to discovering environmental causation that was developed by Dr. Theron Randolph. Randolph originated the idea of an environmental unit employing what he terms "comprehensive

environmental control" as both a diagnostic and therapeutic tool for dealing with these patients. Briefly, this technique involves placing the patient in a specially constructed environment devoid of materials that off-gas, avoiding the use of drugs, cosmetics, perfume, synthetic materials, etc., and having the patient fast for a period of days until symptoms resolve. This initial period of avoidance and fasting requires approximately 4-7 days on the average. During this time, the patient exhibits withdrawal symptoms such as headache, malaise, irritability or depression. At the end of this time, the patient's symptoms, if environmentally related, should clear. Ecologists say this does occur in the vast majority of patients. At the end of this avoidance phase, the patient generally has a markedly lower pulse rate and an increased sense of well-being as well as resolution of symptoms. Next, individual foods are reintroduced, one per meal, and the patient is placed on a rotating diet of "safe" foods (i.e., foods that did not provoke symptoms for that particular patient). Drinking waters from a variety of sources also are tested to find one most compatible with the patient. Finally, the patient is challenged with very low levels (levels routinely encountered in daily living) of common chemicals. Those exposures, both food and chemical, which induce symptoms are to be avoided. A more detailed discussion of comprehensive environmental control follows in Section IVA(3) of this report.

We feel strongly that this operational definition is essential to resolving, once and for all, the debate whether an individual's symptoms are or are not environmentally induced. An environmental unit is necessary for scientific validation of the concept of chemical sensitivity. Because of the expense and time required by patients and physicians alike, we are not arguing that the unit be used for all patients. Nor are such stringent measures necessary for most patients. However, for severe cases there is no alternative at present, and it is only from first-hand observation of hospitalized patients that physicians will have the opportunity to understand this illness better. (This argues for the establishment of [a] demonstration unit[s].) In time, as more clinical data on these patients accumulate, physicians may be able to diagnose this disorder on the basis of the patient's history and a few key laboratory tests. For now, reliance must be placed on rigorous study in an environmental unit.

The environmental unit is the gold standard against which all other diagnostic approaches and screening techniques should be measured. However, most individuals can remain outpatients while they are guided through an elimination diet, avoidance of possible chemical incitants and rechallenge with suspected offenders. An environmental unit is necessary in more severe cases, e.g., those who have failed outpatient attempts at management or for patients with seizures, suicidal tendencies, arrhythmias or other problems requiring continuous vigilance. In a later section, we discuss provocation-neutralization and other office-based techniques that have been adopted by clinical ecologists in order to screen for and treat this illness. An enormous number of diagnostic and therapeutic modalities have been proposed, many of them lacking scientific verification. It is important to separate the gold standard, comprehensive environmental control with the use of an environmental unit, from the "fool's gold" of some of the more outlandish and untested diagnostic and therapeutic modalities. That is not to say that certain of those approaches are not now efficacious

or may not "pan out" in the future, but many await and need critical scientific appraisal.

One aspect of clinical ecology that has repelled many traditional practitioners is the hodgepodge of unscientific, sometimes "new-age", and even spiritual approaches patients with this illness have resorted to in a desperate struggle to restore their health. Randolph himself has expressed dismay at this turn of events. A survey of arthritis patients, who (like the chemically sensitive patient) have limited therapeutic options and may lead constricted lifestyles, revealed that 94% had tried at least one or another unorthodox therapy [Wasner 1980]. From the chemically sensitive patients' viewpoint, searching for alternative therapies is understandable since the available treatments for this problem primarily have been avoidance of exposure and an elimination diet. Restrictive diets and avoidance do not permit full engagement in a modern lifestyle and naturally patients will seek alternatives. To the outside observer, these patients' practices appear "cultist" and members of this supposed cult have been labelled in print as "true believers" and their physicians, "gurus" or "pseudoscientists." We find such terminology unfortunate and counterproductive. It would not appear to reflect the level of intelligence and professional achievements of these patients, many of whom are scientists, doctors, lawyers, teachers and others from whom one would expect a modicum of common sense. Many are very intelligent individuals who are angry at traditional medical practitioners for their unwillingness to study and understand this illness.

As individuals with chemical sensitivities are caught up in the escalating debate among medical practitioners, they find it more and more difficult to obtain unbiased, useful information regarding their condition. This underscores the importance of the operational definition which we have proposed for chemical sensitivity. This definition takes the problem seriously and offers objective, scientific means for its study, i.e, the environmental unit. With regard to other definitions that have been proposed, we agree that Cullen's narrowed, descriptive case definition may have utility in some epidemiologic investigations, for example, in tight-building syndrome or certain occupational outbreaks. However, in dealing with such a diversity of agents causing equally diverse effects at extraordinarily low levels with no true unexposed control group, it may be very difficult to engage in meaningful epidemiologic investigations.

Another term in this controversy which has confused patients and physicians alike is the word "allergy". In a scholarly review, Dr. Alsoph Corwin, Professor of Chemistry Emeritus from the Johns Hopkins University, discusses the historical consequences which have arisen out of what he calls a faulty definition of allergy. He traces the evolution of the term "allergy" and the consequences this has had for the development of the field:

> "Essentially, the fallacy lies in the confusion of hypersensitivity with immunity and the consequent exclusion from consideration of those cases of hypersensitivity which do not exhibit serological abnormalities.

> These include many food reactions, drug allergies and reactions to environmental pollutants." [Corwin 1985]

Corwin acknowledges Randolph and clinical ecologists for not having been hamstrung by the limited definition of allergy as IgE-mediated disease, and for having attempted to document and elucidate the mechanisms of individual hypersensitivity, a problem he describes as much more prevalent than atopy. According to Corwin, "Estimates of the incidence of hypersensitivity in the general population run from 50-90%, whereas only approximately 6% have atopic allergy." The faulty definition of allergy, by excluding most hypersensitivities, has had devastating consequences according to Corwin. He points to the work of Randolph in establishing cause and effect relationships between environmental factors and disease, saying, "Exclusion of these phenomena [that is, restricting the definition of allergy to IgE-mediated disease] also involves the world in tremendous expenditures for research for the elucidation of disease states when the solutions to the problems lie unused in the great medical libraries of the world." (See Section IVC on Health Effects.) Here Corwin is alluding to the writings of Randolph and others.

This view of allergy being limited to IgE-mediated phenomena has had considerable consequence for the practicing traditional allergist. Dr. William T. Kniker, the 1985 Bela Schick Lecturer, a professional honor bestowed by the American College of Allergy and Immunology, described the erosion of the allergist's practice by ear, nose and throat (ENT) physicians, pulmonary specialists, and other groups [Kniker 1985]. Kniker warned his fellow allergists: "We are not yet comfortable with other hypersensitivity diseases (immunologically triggered or not), adverse reactions to foods and environmental factors (occupational, hobby, home)....The narrowness of our specialty makes us extremely vulnerable." He quoted the author of Megatrends who forecast "...the triumph of the new paradigm of wellness, preventive medicine, and holistic care over the old model of illness, drugs, surgery, and treating symptoms, rather that the whole person. The next big shift will be to focus on the environmental influences on health!" [Emphasis by Kniker.]

Randolph estimates that there are nearly 2,000 physicians applying the techniques of clinical ecology, including roughly 900 ENT physicians, in contrast to 3,000 to 3,500 conventional allergists [Randolph 1987, 292]. In many communities there is a surfeit of traditional allergists, and new allergists find demand for their skills waning [Kniker 1985]. Clinical ecologists on the other hand are quite busy. Randolph notes "when there were only a few of us we were treated as a gadflies. Now that we are 40% of the total we are perceived as a real threat and dealt with accordingly" [Randolph 1987, 292]. Almost all of the traditional allergists we interviewed feel strongly that allergy should embrace patients who have heightened reactivity to chemicals and/or foods, irrespective of the etiology of their problem. Selner, in particular, has written:

> "There is every indication that the problem of chemical intolerance will continue to grow. We view these events as an opportunity for Allergy to appropriately expand its interest and influence into areas to which the

> public and the medical profession have traditionally turned to allergists for answers....Although this may require fundamental changes in traditional practice priorities as well as allergy training curriculums, we believe the future of allergy practice can be found within this challenge." [Selner 1985]

Doris Rapp, a board certified allergist who practiced traditional allergy for 18 years, turned to clinical ecology 14 years ago when she observed a dramatic reaction to food in a friend and became intrigued that clinical ecologists almost never placed asthmatic patients on steroids. She feels it is "ludicrous" to say that what ecologists do is not allergy. In her view she always was, still is and will continue to be an allergist:

> "I am doing the same things, for example, that I did for the first 18 years, but much better. I use the same extracts to test and treat. What I do, however, requires much more time, and the overhead is discouragingly increased. But the rewards are that patients, not helped by others, or previously not helped by myself, often get well quickly." [Rapp 1985]

It is ironic that patients with chemical sensitivity who have seen traditional allergists and told them they had an "allergy" to tobacco smoke or some other substance, have been lectured to on the subject of allergy and what its definition <u>really</u> is, i.e., IgE-related disease. Some allergists whom we interviewed told us that they attempt to educate these patients by handing them copies of the position papers of the American Academy of Allergy and Immunology entitled "Clinical Ecology" or "Controversial Techniques" (see bibliography). Patients who consult allergists probably do not care whether what they have is, by definition, an allergy or not; what they are interested in is help in treating an adverse reaction to some substance.

2. <u>Adaptation</u>

One of the difficulties the observer encounters in trying to understand chemical sensitivity is its ostensible lack of a central concept or unifying theory. Such a unifying theory does exist and revolves around the concept of <u>adaptation</u>, known in other contexts as "acclimation" or "acclimatization" and even "addiction" (which we will explain later). Randolph has used the terms "adaptation" and "addiction" most often. However, the reader may find it easier to grasp the concept by reference to one of the other two words. Acclimatization is a widely used term in occupational health and refers to workers gradually becoming accustomed to exposures on the job, for example, heat stress. Understanding adaptation is important here for two reasons: (1) adaptation makes it difficult to discover the effects of a particular exposure on the body and (2) chemical exposures may adversely impact adaptation mechanisms thus leading to illness.

Relatively little can be discovered about "adaptation" by reading medical textbooks or recent major medical journals, in part because of the absence of

Randolph's writings from such publications for a quarter of a century. However, detailed discussions of adaptation appear in all of Randolph's books, in journal articles by him from the 1950's, and in the clinical ecologists' literature. Our impression from interviewing traditional allergists is that many allergists are not aware of this concept and its clinical ramifications.

Concerning adaptation (or acclimation) Randolph wrote:

> "Human ecology embodies the concept of a person's adaptation to the conditions of his existence. The ecologic effects of chemical incitants are observed most advantageously by first isolating an individual from the total chemical environment and then observing his response to re-exposure to previously avoided parts of it." [Randolph 1962, 5, emphasis by Randolph]

That human beings respond to chronic exposure to environmental challenges by adapting, acclimating, acclimatizing, or even becoming addicted is widely recognized for a variety of substances. Most would agree that the use of narcotics, alcohol, nicotine and even caffeine can be addicting. For example, the first cigarette might be associated with some eye and throat irritation but over time, with more cigarettes, most individuals adapt to this and only the pleasurable effect of nicotine on the brain might be experienced. After months or years, more cigarettes (or alcohol or caffeine or drugs) may be required for the same amount of "lift." The individuals may exhibit addictive behavior seeking cigarettes more frequently. Subsequently, quitting cigarettes (alcohol, caffeine, or drugs) may lead to "withdrawal symptoms" including irritability, drowsiness, fatigue, moodiness, headache, etc. After individuals have quit smoking, they may find themselves "supersensitive" to the smoke of others (the forgotten eye and throat irritation reappear after a period of avoidance). This example parallels the food and chemical adaptation and addiction that ecologists like Randolph have described in their patients. Frequent exposure to a substance results in adaptation (e.g., irritation/warning signals may disappear). With continued exposure thus may lead to addiction. Reduction or cessation of exposure generally results in withdrawal symptoms.

The difference between chemical exposures and cigarettes, alcohol, or caffeine is that in the former case addiction is an unwitting process. The individual may have no idea it is occurring. But if the offending chemical is removed, withdrawal symptoms may ensue (similar to those listed above--c.f. Table IV). With reexposure to the substance following a period of avoidance, symptoms return, often quickly and much more obviously related to the exposure. Here is what is confusing to many patients and practitioners: the symptoms for which the individual is most likely to seek a physician's help are those that occur during withdrawal when the person is no longer exposed (or less exposed) to the offending agent! Thus headaches may occur when the individual smokes fewer cigarettes than usual or drinks less caffeine. Indeed, these unpleasant withdrawal symptoms may be forestalled by smoking another cigarette or taking another drink of coffee or alcohol, perpetuating addiction. Patients may report that smoking a cigarette or drinking a cup of coffee in the morning (after

eight or so hours without) relieves their headache (a withdrawal symptom) and they feel better, not suspecting that these might also be the cause of their headache.

There are also many examples from occupational health in which acclimatization or inurement or tolerance to a substance is known to develop, for example, exposure to ozone, nitroglycerin, cotton dust, welding fumes (containing zinc), solvents and others. Note that the incitants mentioned thus far are all quite different from one another: some are ingestants, others inhalants; some are solid, others liquid or gaseous in form; some are organic, others inorganic; some (ozone) are simple inorganic molecular gases, while others (welding fumes) are complex mixtures of organic and inorganic substances in solid, liquid and gaseous phases. The point is that the human organism has the capacity to adapt to an endless array of substances. In the extreme, as described for cigarettes and caffeine, individuals unknowingly may become addicted to the incitant. Addiction is most likely to be recognized for substances which have euphoric or other pleasant properties, e.g. drugs, caffeine or nicotine, and less likely to be recognized for chemicals and foods without these properties.

By isolating his patients from their usual environments and then re-exposing them, one-by-one, to various foods and chemicals, Randolph discerned that adaptation plays an important role in many common substances people eat, drink or inhale. Virtually any food or chemical follows the same pattern: initially, the individual notes symptoms when the substance is first encountered; gradually, with continued exposure or multiple re-exposures, tolerance or adaptation or acclimatization occurs. However, adaptation or "addiction" to commonly eaten foods, such as corn, wheat, milk, eggs, citrus fruit, or to common chemical inhalants, e.g., formaldehyde or gas combustion products, while generally not recognized by patients or their physicians, also occurs, according to ecologists.

As we indicated earlier, what Randolph contributed was a systematic approach to studying individual responses to foods and chemicals. By removing individuals from their total background of environmental incitants and exposing them one-by-one to each food and each chemical, he was able to observe a bi-phasic response to some of these substances (see Figure 6). He noted that initially, the individual might experience a stimulatory effect (adapted response; tolerance develops) lasting varying periods of time depending upon the incitant. However, this "up" phase was generally followed by a withdrawal phase (maladapted response; loss of tolerance). When the individual began to experience unpleasant withdrawal symptoms that he would seek, consciously or unconsciously, more of the same substance. These ups and downs follow a sort of sinusoidal (bi-phasic) pattern as depicted in Figure 6. On the graph, beginning at zero, the patient is free of symptoms and at baseline health status. Following a one-time or occassional exposure to a provoking substance, stimulatory effects result; after a period of time (minutes to hours to days depending upon the nature of the incitant) the stimulatory effects subside, giving way to withdrawal symptoms. The frequency of these up and down reactions depends upon the frequency of the person's contact with the incitant. The amplitude of the stimulatory and withdrawal portions of the reaction depend upon the substance and the

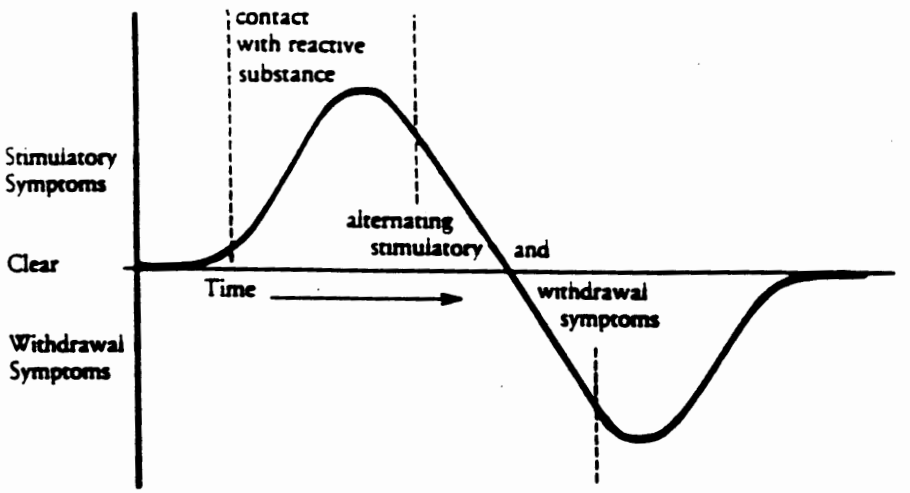

Figure 6: Symptom Progression of
a Single Reaction to an Incitant

During the early phases of exposure to a particular substance, stimulatory symptoms predominate ("up," "hyper," jittery). As exposure to the offending agent continues, adaptation occurs and fewer of these symptoms are experienced. With removal from (or discontinuance of) exposure, the individual experiences withdrawal symptoms ranging in intensity from mild to severe (see Table IV).

Source: O'Banion, D.R., Ecological and Nutritional Treatment of Health Disorders, Springfield, Illinois: Charles C. Thomas, Publisher, 1981, p. 68, quoted in I. Bell, Clinical Ecology, p. 26.

individual's susceptibility (degree of adaptation or addiction) to it. For example, an occasional drinker, or a painter exposed to solvents the first few times, might have a relatively pleasant "up" phase with relatively few withdrawal symptoms afterward. On the other hand, as exposures become more frequent, "addiction" may occur. A painter might visit other painters on his day off in order to "sniff" some solvent [Randolph 1987,109]; perhaps drinking alcohol has a role in forestalling solvent withdrawal symptoms in some susceptible painters.

The key to understanding multiple chemical sensitivity is recognizing these ups and downs that occur after exposure to many different substances. Table IV [Randolph 1980, 30] illustrates the pattern of reaction Randolph claims he has observed in thousands of patients after exposure to an incitant. The amplitude of a reaction varies from person to person and incitant to incitant, but the pattern is quite constant. Beginning in the center of the table at zero, read upward for stimulatory effects and down for withdrawal effects. Note that many of the stages, both stimulatory and withdrawal, are characterized by central nervous system (CNS) symptoms, e.g., anxiety, confusion, depression and irritability. Such symptoms are commonly noted by patients with multiple chemical sensitivities. The early stimulated (+ and + +) levels are adaptive responses by the body to an environmental incitant. Individuals at adaptation level + are stimulated but relatively free of symptoms. They may remain at this relatively desirable level (which often is confused with normalcy, level 0) indefinitely. According to Randolph, individuals rarely seek medical help at levels + or + +. However, the onset of withdrawal (-) symptoms, whether systemic (e.g., fatigue, myalgia, or impaired concentration) or localized (e.g., rhinitis, asthma, or colitis), brings patients to the doctor. Often, the plus (+) phase of any reaction is followed by a minus (-) phase at least as intense, or perhaps one stage deeper. Thus a + + stimulatory phase may be followed by a -- or --- withdrawal phase (see Table IV). In many individuals, every step of the entire sinusoidal progression of symptoms (e.g., +, + +, +, 0, -, --, --- and finally back up to --, - and 0) can be observed. The most extreme case would be progression from mania to deep depression in a single patient, as in manic-depressive disease. Another interesting aspect is the tendency for psychotic (+ + + + or ----) and allergic (- and --) manifestations to alternate in individuals. In the 1800's Savage described several cases in which insanity alternated with asthma; when one was present, the other disappeared. Old psychiatric texts refer to this vacillation between physical and mental manifestations as "alternation" [Randolph 1976b].

With long-term exposure to a given incitant (e.g., alcohol), especially in certain individuals, the degree and duration of stimulation may become less and less while the withdrawal or depressed phase becomes deeper and more prolonged. At face value, this sinusoidal reaction to a substance might seem a somewhat artificial construct, but Randolph asserts it is not. Randolph himself has hospitalized, fasted and tested over 10,000 persons with many foods and chemicals since 1956 and his theories are distilled from observations of patients who have gone through an environmental unit [Randolph 1980, p. 169]. For a patient with sensitivities involving foods alone, an elimination diet, or fasting followed by reintroduction of single foods may be adequate for diagnosis. However, since WWII, Randolph states that he has observed increasing

Table IV
Stimulatory and Withdrawal Symptoms Associated with Exposure to Various Foods and Chemicals
Source: Randolph 1980, p. 30

Begin at 0 (normal behavior, feeling well, and follow the stimulated levels (+ up to ++, +++, etc.) which result from exposure to a particular substance (tolerance or adaptation is occurring during these stages). With removal from exposure, the individual withdraws (+++, down to ++, +, 0, -, --, etc.) and experiences symptoms of withdrawal (loss of tolerance, or maladaptation).

STIMULATED	Maladapted Cerebral and Behavioral Responses	++++ MANIC, WITH OR WITHOUT CONVULSIONS	Distraught, excited, agitated, enraged, and panicky. Circuitous or one-track thoughts, muscle-twitching and jerking of extremities, convulsive seizures, and altered consciousness may develop.
		+++ HYPOMANIC, TOXIC, ANXIOUS, AND EGOCENTRIC	Aggressive, loquacious, clumsy (ataxic), anxious, fearful, and apprehensive; alternating chills and flushing, ravenous hunger, excessive thirst. Giggling or pathological laughter may occur.
	Adapted Responses	++ HYPERACTIVE, IRRITABLE, HUNGRY, AND THIRSTY	Tense, jittery, "hopped-up," talkative, argumentative, sensitive, overly responsive, self-centered, hungry, and thirsty; flushing, sweating, and chilling may occur, as well as insomnia, alcoholism, and obesity.
		+ STIMULATED BUT RELATIVELY SYMPTOM-FREE	Active, alert, lively, responsive, and enthusiastic, with unimpaired ambition, energy, initiative, and wit. Considerate of the views and actions of others. This usually comes to be regarded as "normal" behavior.
"NORMAL"		0 BEHAVIOR ON AN EVEN KEEL, AS IN HOMEOSTASIS	Calm, balanced, level-headed reactions. Children expect this from their parents and teachers. Parents expect this from their children. We all expect this from our associates.
WITHDRAWAL (MALADAPTED) RESPONSES: LOSS OF TOLERANCE	Maladapted Localized Responses	– LOCALIZED ALLERGIC MANIFESTATIONS	Running or stuffy nose, clearing throat, coughing, wheezing. Asthma, itching (eczema and hives), gas, diarrhea, constipation (colitis), urgency and frequency of urination, and various eye and ear syndromes.
	Maladapted Systemic Responses	-- SYSTEMIC ALLERGIC MANIFESTATIONS	Tired, dopey, somnolent, mildly depressed, edematous with painful syndromes (headache, neckache, backache, neuralgia, myalgia, myositis, arthralgia, arthritis, arteritis, chest pain), and cardiovascular effects.*
	Maladapted Advanced Stimulatory Responses	--- BRAIN-FAG, MILD DEPRESSION, AND DISTURBED THINKING	Confused, indecisive, moody, sad, sullen, withdrawn, or apathetic. Emotional instability and impaired attention, concentration, comprehension, and thought processes (aphasia, mental lapse, and blackouts).
		---- SEVERE DEPRESSION, WITH OR WITHOUT ALTERED CONSCIOUSNESS	Unresponsive, lethargic, stuporous, disoriented, melancholic, incontinent, regressive thinking, paranoid orientation, delusions, hallucinations, sometimes amnesia and coma.

* Cardiovascular manifestations, including rapid or irregular pulse, hypertension, phlebitis, anemia, and bleeding and bruising tendencies, may occur at any level.

numbers of individuals who respond adversely to the chemical environment. Subtle chemical sensitivities may be difficult to assess while a patient remains at home or even in most hospitals, since these generally contain background low levels of natural gas, disinfectants, perfumes, cleaners, tobacco smoke, paints, varnishes, adhesives, and other substances. According to Randolph, the patient's symptoms may be "masked" by the presence of these contaminants (more on this subject will follow).

With regard to chemical sensitivity (or "susceptibility," a term Randolph prefers in order to avoid confusion with classic, IgE-mediated allergic sensitivity), Randolph notes, that more than foods, chemical exposures are:

> "...associated with higher degrees of individual susceptibility and relatively greater persistence of susceptibility as well as more advanced clinical syndromes. Also, once individual susceptibility to one or a few environmental chemical exposures has developed, it almost invariably tends to spread to involve other combustion products and derivatives of gas, oil and coal...." [Randolph 1987, 78]

The stimulatory and withdrawal levels for foods and chemicals overlap each other (see Figure 7) so that in real life, outside of an environmental unit, at any given moment what the organism is feeling is a summation of all of the effects, whether stimulatory or depressive, of the substances he has inhaled, contacted or ingested. From Figure 7, it is clear that attempts to discern the effects of single substances would be frustrated by the overlapping responses. Only by placing the individual in an environment devoid of chemical and food incitants is one able to determine whether his illness improves. Assuming he improves (again this occurs in the majority of cases according to ecologists), the next step is to re-expose him to individual substances in order to avoid overlapping responses and observe the result. According to Randolph, only in this way is one is able to discern the stimulatory and withdrawal phases associated with a given substance. If one does not remove all possible food and chemical contributors, an effect may be missed. Hence, in order to rule out environmental illness definitively, an environmental unit would be required. One can "rule in" environmental illness on an outpatient basis, but not rule it out. Environmental factors should be ruled out first before psychiatric diagnosis and labels are applied to a patient (see later discussion on psychiatric mechanisms).

In real life, stimulatory and withdrawal reactions are observed but often not understood. For example, an asthmatic might feel well after spending a week on a Caribbean island, breathing relatively uncontaminated air and eating a diet devoid of his usual foods, only to have a severe, life-threatening asthmatic response to exhaust from the engine of a boat taking him home. Once back home in his metropolis, he re-adapts, acclimatizes to the auto exhaust combustion products and other air pollutants in his area and experiences only chronic wheezing. Thus, following de-adaptation (removal of incitants), the individual exhibits a more acute and convincing reaction upon re-exposure. This may be what occurs in an environmental unit during testing. So acute and convincing are some of these reactions that patients themselves erroneously (at least in the eyes of some) surmise they must have an "allergy" to a

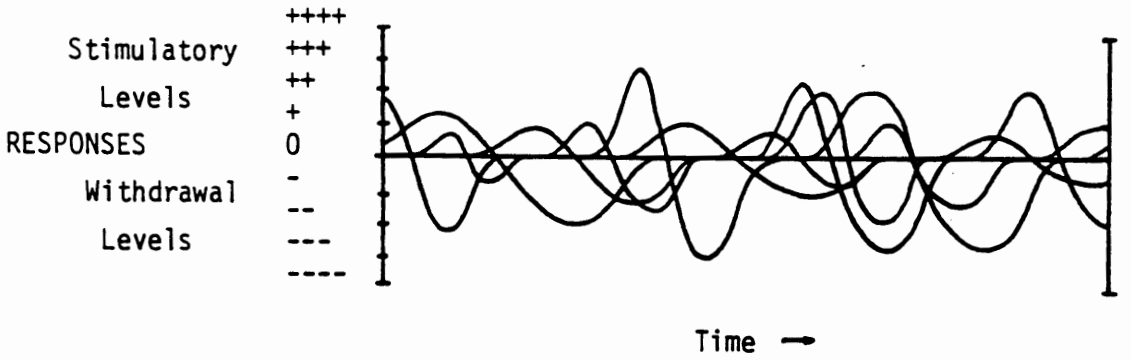

Figure 7: Overlapping of Responses to Food and Chemical Incitants in an individual with multiple exposures and multiple chemical sensitivities. It is difficult in such a case to relate particular exposures to particular symptoms, unless all contributory exposures are eliminated simultaneously and single incitants are tested one-at-a-time.

particular substance. However, if the patient is not de-adapted (unmasked) at the time he is tested, a reaction may not occur, convincing his physician that the "allergy" was all in his patient's mind. Many "double-blind" studies by allergists and others in the past have not taken this phenomenon of masking into account and therefore may be flawed. The sensitivity, if not tested for in the unmasked state, may easily be missed.

In occupational health, there are many widely recognized examples of adaptation that are analogous. They, too, fit a bi-phasic pattern. Industrial hygienists and occupational health physicians know that one of the most valuable clues to work-related illness is a history of intense symptoms following return to work after a vacation or weekend (leading to withdrawal and de-adaptation). The following examples help underscore the existence of this phenomenon of adaptation. These particular examples may or may not also represent multiple chemical sensitivity. It is conceivable that individuals who are more sensitive or susceptible to the following substances may be the same individuals who are prone to developing multiple chemical sensitivities. In other words, multiple chemical sensitivities may reflect failure of adaptation in some sense. Failure may be the result of individual tendencies, an environmental insult, or some combination of the two. Bearing in mind that multiple chemical sensitivity might be what is actually occurring in the most sensitive subgroups exposed to these substances, let us now turn to some specific examples:

1. Welding on galvanized metal causes evolution of zinc oxide fumes which, when inhaled, provoke an influenza-like syndrome with headaches, nausea, weakness, myalgia, cough, dyspnea, and fever. The same symptoms may result from inhaling fumes of copper, magnesium, aluminum, and other metals. Hunter writes:

> "The frequency and severity of the attacks are affected by the regularity of exposure for those who work continuously in the trade seem to acquire a tolerance which, however, is only transient, since it may be lost during a weekend away from work. In such cases the relapse of symptoms after working on a Monday gives rise to the name 'Monday Fever.'" [Hunter 1978, 407]

Thus removal from exposure (de-adaptation) for a couple of days is followed by an exacerbation of symptoms upon return to work.

2. Cotton [Hunter 1978, 1043-1045], grain, and other organic dusts, as well as vapors from contaminated humidifiers also produce an acute flu-like illness, usually on the first work day after a period away from the job. In other words, after a period of de-adaptation, re-exposure to organic dust or vapors may provoke acute symptoms. In both of the examples noted abovve, metal fume fever and flu-like illness from organic dust exposure not just respiratory symptoms appear. Flu-like symptoms involving multiple systems occur in a subgroup of exposed workers.

3. Nitroglycerin, used to manufacture gun powder, rocket fuels and dynamite may cause severe headaches, breathing difficulty, weakness, drowsiness, nausea and vomiting, as a result of inhalation. Lesser symptoms may appear with oral administration, e.g., as a drug for cardiac patients, or with skin contact. Even wives of nitroglycerin workers who launder and iron their husbands' clothing may experience similar symptoms, headache being the most prominent. However, both workers and their wives become accustomed to exposure unless removed from it for two days or longer.

> "The headache may continue for one or two hours, or even for three or four days. The onset may be associated with exhilaration, but usually this passes and the victim becomes depressed.... Tolerance to exposure develops after three or four days of continued exposure, but is lost after two days away from work. Since the 19th century, workers have been known to avoid the Monday headache, once they become tolerant to nitroglycerin, by placing nitroglycerin under their hatbands over the weekend, or sucking occasionally on a piece of dynamite. Others inhaled the fumes from their work clothes over the weekend." [Daum 1983, 639-648, emphasis added]

Stimulatory (exhilaration) and withdrawal (depressed) symptoms occur in a bi-phasic manner. Alcohol may make dynamite headaches worse, cause confusion, extreme agitation, hallucinations or violent behavior; individuals have even been known to commit murder [Daum 1983]. Here then is an example of an individual exposed to a particular chemical who exhibits reduced tolerance for an ingestant (alcohol).

Most studies have failed to show a difference in blood pressure between dynamite workers and controls, however, differences are noted between pressures taken in dynamite workers on Monday (lower) and those taken later in the week. Without insight into the principles of adaptation, one might overlook or discount such a phenomenon, and look only at the average blood pressure during the week. Nitroglycerin has other effects on the central nervous system such as mania (+ + + +), epilepsy (+ + + +), depression (--, ---, ----), aphasia (---), parasthesias (--), as well as headaches (--). Understanding adaptation, one could trace all of these symptoms through their stimulatory and withdrawal levels.

Noteworthy is a study by the Pennsylvania Department of Health of dynamite workers with sudden death, felt to be cardiovascular in origin, almost all of whom died after a period away from exposure on the job (during the withdrawal phase [see footnote in Table IV regarding cardiovascular manifestations]) [Carmichael 1963]. Most of these workers were 30-45 years old and their physical exams were largely unremarkable. "Monday morning angina" has been described among dynamite workers and if their angina attack

does not interfere, returning to work may cure it! The incidence of sudden death among workers at one dynamite plant was 15 times the expected rate. The mechanism for this is unknown; however, some have speculated that acclimatization followed by vasospasm on withdrawal from exposure suggests an increased sympathetic nervous system output compensatory mechanism [Daum 1983]. William Rea, a cardiothoracic surgeon and ecologist, has written extensively concerning arrhythmias and coronary vasospasm, both of which he feels may contribute to sudden death, resulting from food and/or chemical sensitivities [Rea 1981, 1987b].

Hunter relates the story of a dynamite worker who had severe headaches and whose wife and children had terrible headaches as well. His physician recommended slipping two or three grains of powder under his hatband and taking a few more grains and hiding them around the house. This worked well; their headaches disappeared. However, anyone who would come to the house as a visitor would get "a hell of a headache." Of interest is the fact that Alfred Nobel, inventor of dynamite and founder of the Nobel prize, likewise suffered from dynamite headaches over many years. Hunter notes that individual susceptibility to nitroglycerin varies tremendously. In all but two or three percent of workers, tolerance is acquired within a few days of exposure [Hunter 1978, 560-566]. This 2-3% who fail to develop tolerance to nitroglycerine may have the chemical susceptibility (multiple chemical sensitivity) problem.

4. Ozone, an air pollutant of special concern to residents of Los Angeles and other cities has been the focus of considerable research relevant to adaptation. Intrigued by how little respiratory illness and death occurred relative to the high levels of ozone in very polluted cities like Los Angeles, and suspecting adaptation might play a protective role, Hackney et al compared the responses of four Canadians (not adapted) and four Californians (adapted) to ozone challenges [Hackney 1977a]. While reactivity varied greatly from individual to individual, Californians were only minimally reactive to levels that for the Canadians caused coughing, substernal discomfort and airway irritation, pulmonary function test decrements and increased red blood cell fragility.

In another experiment, six volunteers with respiratory hyper-reactivity were placed in an environmental chamber with ozone at typical ambient levels (0.5 ppm) for four days [Hackney 1987b]. Five of six had decreased pulmonary function during days 1-3, but gradually improved, almost to baseline by day 4, suggesting adaptation had occurred. The authors note that not all adverse effects of ozone may be prevented by this adaptation, e.g., increased blood cell fragility may persist. Thus adaptation or masking of some symptoms may occur while other physiological alterations continue.

Because some tolerance to ozone can be induced in small rodents exposed to 1 ppm of ozone in as little as one hour, Stokinger speculated that the mechanism that seemed to explain observations in animals best was "either

a cellular depletion phenomenon or enzyme stimulation" [Stokinger 1965]. Mustafa, discussing oxygen (as opposed to ozone) toxicity cautions "...[t]he term 'tolerance' should not be considered to indicate absolute tolerance, because continuing injury does occur, and eventually, emphysema-like changes and fibrosis develop." In the short-term, tolerance may be protective, but "...when exposures are continuous or intermittent for a period of weeks or even years, it is likely that unacceptable lung injury is necessary to keep the mechanism of tolerance or adaptation activated" [Mustafa 1978]. With regard to ozone exposures among "adapted" Southern Californians, Mustafa comments, "Whether or not they have continuing lung injury with increased probability of bronchitis, emphysema, or even malignancy is not known, although some reports have supported the concept."

Bell, extending these ideas to chemically sensitive patients speculates that their chronic symptoms "may reflect the more insidious, non-adapting changes induced by offending foods and chemicals. At the same time, the more obvious and dramatic adverse clinical effects may be masked or adapted" [Bell 1982a].

We have mentioned only a few of the "exposures" that are recognized as involving adaptation: alcohol; nicotine; caffeine; various drugs; metal fumes; organic dust; nitroglycerine; and ozone. What is clear is that individuals with or without multiple chemical sensitivities undergo adaptation to a wide variety of substances in their environment. What is not clear is the specific role adaptation plays in the dramatic responses patients with food and chemical sensitivities have to low-level exposures that do not overtly affect others (for further discussion see Section VA on Possible Mechanisms).

Without exception, all of the traditional allergists whom we interviewed recognized the phenomenon of acclimatization or adaptation and agreed that it was potentially a crucial variable that should be controlled in studies of low-level exposure to chemicals. These concepts are familiar to occupational health practitioners and industrial hygienists because they observe such effects first-hand among workers exposed to chemicals. Randolph states that most physicians see patients long after adaptation has occurred and end organ damage is setting in: "It is much as if the physician arrived at the theatre sometime during the last scene of the second act of a three act play--puzzled by what may have happened previously to the principal actor, his patient" [Randolph 1962, 7]. Through comprehensive environmental control, i.e., an environmental unit, one can overcome the masking effect of adaptation and "back up" or reverse the exposure allowing one to monitor toxicity in progress. The environmental unit represents a kind of dynamic toxicology; traditional medical approaches provide only a snapshot of what is happening to the patient.

The sheer heterogeneity of substances that can evoke adverse reactions, (those enumerated above and others) suggests a fundamental mechanism of adaptation to environmental substances. This may well involve the nervous system or some system(s) other than the immune system. (See later discussion in Section VA.)

However, the net effect resembles a classic allergic response, that is, an untoward reaction to an incitant. This is a concept that has clinical utility.

Since adaptation appears to be a generalized response [Selye 1956], it is not inconceivable that a toxic insult, e.g., to the sympathetic nervous system or to enzyme detoxification pathways, could cause a general loss of the ability to adapt to a wide variety of substances, including other chemicals and even foods (the spreading phenomenon). Knowing the mechanism by which this occurs would, of course, be ideal. Thus far, it has eluded clinical ecologists, placing them at distinct disadvantage.

Observing a phenomenon and documenting its existence must, of necessity, precede knowledge of its mechanism. Of course, it is not necessary to know the mechanism of a disease in order to prevent it. An historic example of this occurred in 1854 when a physician in London, Dr. John Snow, noted that individuals who developed cholera obtained their drinking water from the Broad Street pump. Medical folklore has it that by ordering the removal of the pump handle, he stopped the epidemic [Snow 1936]. It was not until 1883, almost thirty years later, that Koch discovered the bacterium responsible for cholera. Analogous to the current dilemma, it is not necessary to understand the mechanism for food and chemical sensitivities in order to begin treating them. Eventually, knowledge of the mechanism may suggest better treatments.

With regard to patients with chemical sensitivities also developing dietary intolerances, Bell notes that "foods are not only sources of nutrients, but also complex mixtures of organic chemicals. For instance, it is the unique pattern of chemical constituents that make a tomato a tomato rather than an apple" [Bell 1982b, 35-36]. She provides a partial listing of chemical constituents of tomato, apple, milk and orange. Allergists Butcher, Salvaggio et al reported an interesting case of a worker with toluene di-isocyanate (TDI) sensitivity who was also intolerant of radishes [Butcher 1982]. Both TDI and radishes contain allylisothiocyanate and benzylisothiocyanate, but other foods containing these same chemicals did not provoke symptoms. The authors were unable to speculate as to the possible mechanism for this cross-sensitivity.

McGovern has also written about chemical and food cross-sensitivity and noted that many foods contain phenolic derivatives [McGovern 1981]. Chemically sensitive patients also frequently react to phenolic inhalants. McGovern attempted to desensitize patients to particular phenolics and noted very robust reactions to such challenges. Rea reports food sensitivities in 80% of his patients with chemical sensitivities [Rea 1988a]. Like airborne pollutants, foods contain a wide range of chemical constituents and are in intimate contact with the organism for long periods of time. The surface area of the gastrointestinal tract is enormous and the chemical load, both in terms of quantity and diversity of exposure, is huge.

To summarize, it appears that adaptation may initially be a substance-specific response which can subsequently affect the organism's overall ability to adapt to other

substances. The mechanism is unknown but not crucial to our recognition of or intervention in this problem. Finally, the use of an environmental unit provides a way of unmasking or "backing up" the experience, or, as Randolph states, provides "the means of reverting many chronic illnesses of unknown cause to acute illness in which specific etiology is readily demonstrated" [Randolph 1976a].

3. The Environmental Unit

The above discussion has been a necessarily detailed description of a very difficult concept. Adaptation and the use of an environmental unit are such detailed and comprehensive topics that they do not lend themselves to the short presentations typical of most scientific forums. Yet, physicians must understand adaptation if progress is to be made in this field. Some of the allergists we spoke with recognize the pivotal role adaptation may play. Prominent among them is Dr. John Selner, an allergist who has long advocated that allergists take a more active role in understanding patients with alleged chemical sensitivities and who described in detail the design and operation of an environmental unit [Selner 1985a]. Selner visited Rea's unit in Dallas and collaborated with Ken Gerdes, an ecologist who trained with Randolph, to establish a unit in Denver at Presbyterian-St. Luke Hospital in 1979. This unit, which operated for several years before closing for reasons unrelated to its utility as a diagnostic tool, incorporated many if not most of the features of existing clinical ecology units. Rea and Randolph, who had their own units, both visited Selner's unit when it opened and admired the care that had been exercised in its construction. Without exception, all of the allergists with whom we spoke agreed that an environmental unit like Selner's was an important tool for properly evaluating patients with alleged low level chemical sensitivities. Few, however, appreciate the degree to which Selner patterned his approach after that developed by the clinical ecologists.

Both the clinical ecologists' environmental units and Selner's unit shared many, if not most, of the same design and operational parameters. (See Table V.)

We are unable to discern any major differences in these two approaches. Even though Selner's unit is no longer in operation, he continues to employ some of the same principles, e.g. housing patients in a relatively clean environment to help avoid chemical exposure prior to testing. In Selner's view, the fundamental concept is still valid. He states, as do Rea and Randolph, that the majority of patients can be worked up as outpatients. However, there is a small percentage who are difficult to evaluate without such a facility.

Studies from the ecologists' units leave much to be desired in terms of study design. Unfortunately, no studies were ever published from the allergists' unit in Denver. Every traditional allergist whom we interviewed recognized that removal from exposure prior to testing might be a critical factor in studying reactions to low levels of chemicals. They felt that re-establishment of a unit would be an important

Table V

FEATURES OF ENVIRONMENTAL UNITS*

Characteristics/Practices	**Allergists' Unit** (Selner in Denver, CO) [Selner 1985a]	**Clinical Ecologists' Units** (Randolph in Chicago, IL, and Rea in Dallas, TX)
Construction using materials that do not off-gas, (primarily glass, steel, ceramic, cotton bedding and clothing). Avoidance of synthetic materials. No perfumes, cosmetics, odorous cleaners/soaps, etc.	Yes	Yes
Air supply filtered; patients' rooms under positive pressure to reduce contamination from adjacent areas; airlocks	Yes	Yes
Patients' medications discontinued in so far as possible; gradual withdrawal from steroids, etc.	Yes	Yes
Patients fasted for 4 to 8 days to clear symptoms	Yes, if symptoms do not clear after several days in unit	Yes, at time of admission to unit
Organic foods used for food testing; commercial foods tested also	Yes	Yes
Patients tested for acceptable water	Yes	Yes
Challenges performed using single foods and chemicals after period of avoidance (to eliminate masking)	Yes	Yes

* None of the units described in this table is currently in operation.

step in understanding the problems of individuals who believe they are sensitive to low levels of chemicals. In fact, some of the allergists offered examples where removal from exposure for several days prior to testing would be important, such as exposure to western red cedar or cigarette smoke. They were not at all opposed to the concept of an environmental unit and were aware of the not inconsiderable expense involved in establishing a well-designed and well-run environmental unit.

Some allergists we interviewed felt ecologists should be involved in the design of a study unit and appropriate protocols because of their experience in this area and so as to avoid later criticism from the ecologists regarding the protocols that are used. Two of the traditional allergists whom we interviewed praised Rea's engineering skills in designing and operating his unit, one saying, "No one does it as well as Rea does." Rea has, in fact, stated his willingness to cooperate with any impartial venture to undertake studies using his facilities or to design a model research unit elsewhere.

The detailed description of an environmental unit is beyond the limits of this discussion. However, to illustrate the degree of environmental control which Rea has achieved, we reproduce the following data from his environmental unit. Figures 8 and 9 depict ambient air concentrations, in parts per million of ozone and nitrogen dioxide, respectively. Solid lines represent concentrations inside the Dallas environmental unit; dotted lines are outdoor ambient air concentrations; broken lines are concentrations from the corridor leading to the unit.

Impressively low levels of airborne contaminants are achieved by Rea inside the unit. Further, by employing construction materials, furnishings and clothing that are less likely to off-gas, very low levels of volatile organic compounds (e.g., from synthetics) can be maintained inside the unit. To create and operate a unit that is as free as possible of chemical pollution requires knowledge, precision and vigilance while working with architects, ventilation engineers, contractors and their suppliers, nurses, dieticians, food and water suppliers, maintenance and custodial staffs. Obviously, "this is no trifling undertaking" [Selner 1985a].

More than 25 years ago, Randolph wrote that the environmental unit is an approach to studying disease that supplements the other well-known approaches used in medicine. In general, there are basically three scientific approaches for studying a disease: (1) clinico-pathologic studies, (2) animal experiments, (3) epidemiologic investigations.

To these, Randolph has added a fourth tool, comprehensive environmental control. There are major limitations inherent in using animal models, clinico-pathologic studies and epidemiologic investigations to study the phenomenon of multiple chemical sensitivities. None is as sensitive to low-level exposures and effects as the use of an environmental unit where all exposures are controlled simultaneously and the individual is challenged with single substances while in the de-adapted state.

Animal models are best used to study relatively high doses of chemicals that result in distinctive physical or biochemical pathology that can be monitored. First an

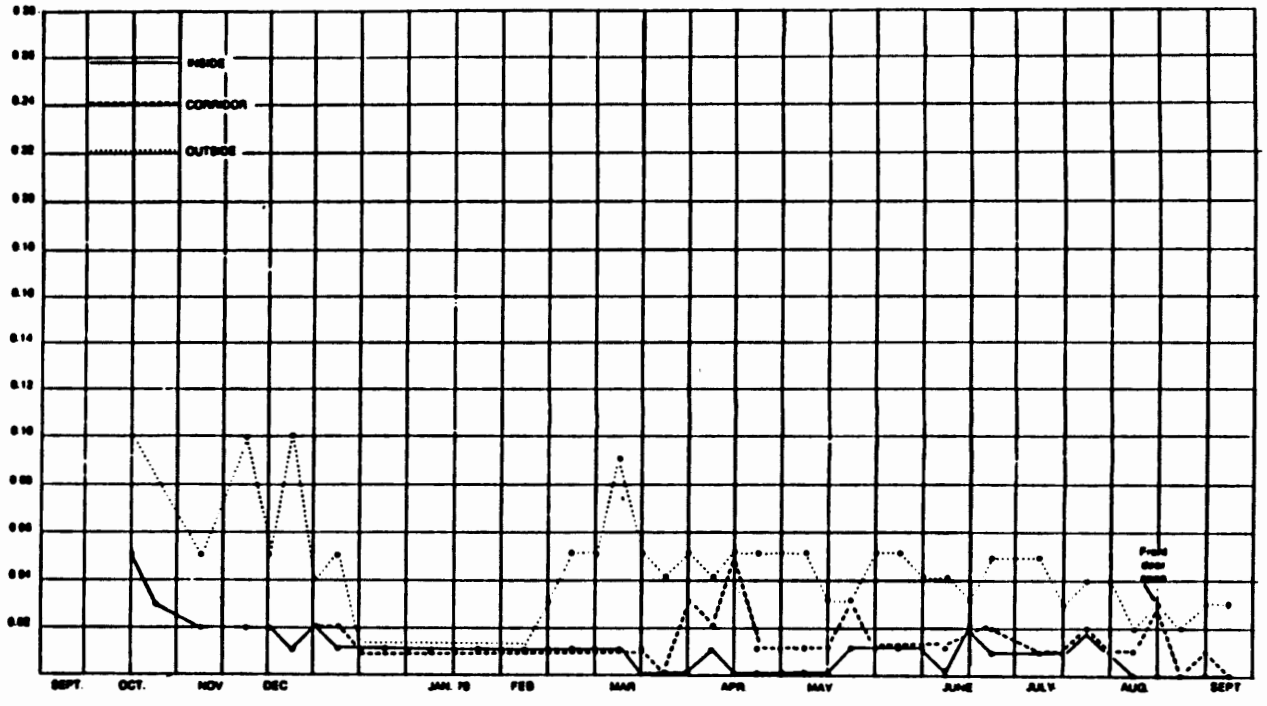

Figure 8: Graph depicting measurement of ozone in specially constructed rooms. Source: Rea 1987b.

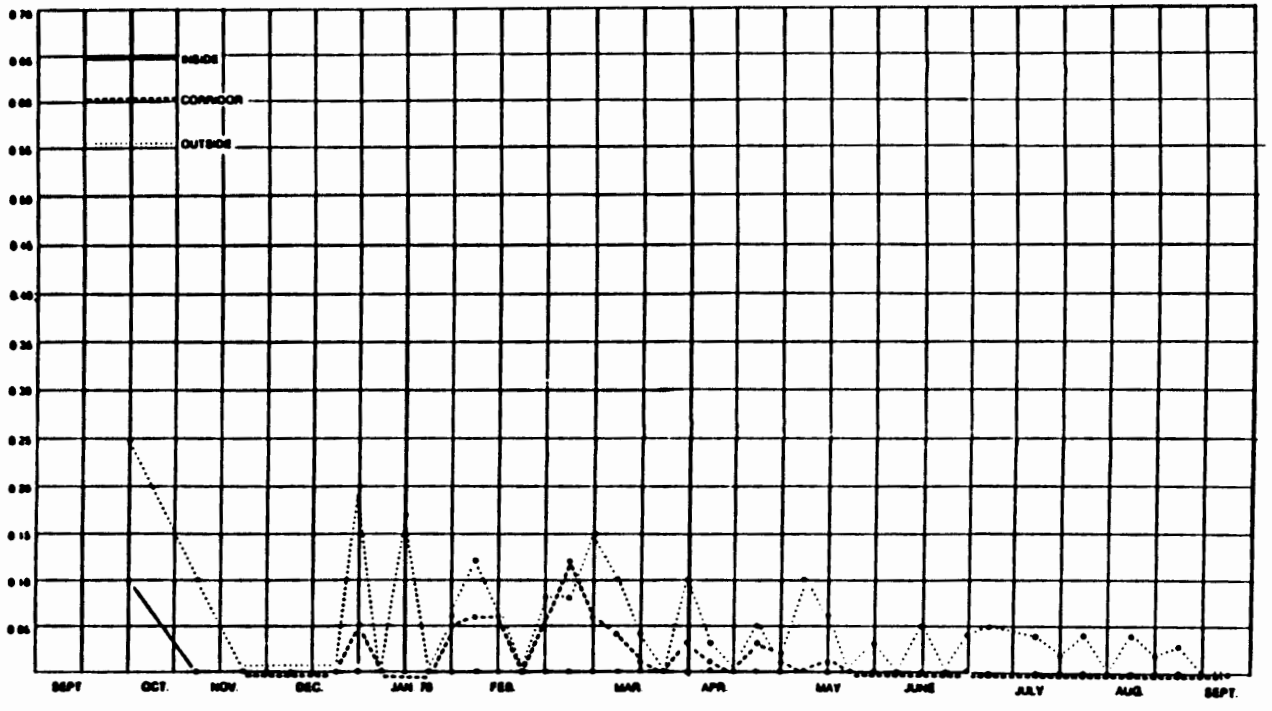

Figure 9: Graph depicting measurement of nitrogen dioxide in specially constructed rooms.
Source: Rea 1987b.

appropriate animal must be found. Then, there are always concerns about extrapolations to humans; but more importantly here, rats, mice and other animals are unable to tell you if they have a headache, feel depressed or anxious or are nauseated. Thus the subtle effects of low-level chemical exposure may be missed entirely.

Epidemiology may have some utility with regard to tight buildings or community exposures to a toxic material. If everyone in the population responds with the same symptoms to the same agents, the task is relatively easy. However, if some persons have headaches, others have muscle spasms, and still others are less able to concentrate, and so on, the results blur and may wash out entirely, i.e., no single symptom has a statistically significant prevalence over controls. Thus, for multiple chemical sensitivities with multiple triggers and multiple health effects, epidemiology may be an insensitive tool. Further, although epidemiology can point to associations between events, other kinds of studies are needed to establish cause and effect relationships. In the study of chemical sensitivity, identification of an unaffected control group presents further difficulties.

Clinico-pathologic studies rely upon the presence of some clinical sign (e.g., tachycardia or decreased reflexes), laboratory measurement or tissue pathology. For meaningful data in man, large numbers of similarly exposed individuals with similar end-organ effects must be examined. Again, multiple chemical sensitivities may involve multiple triggers and multiple effects. To date, no single laboratory test is abnormal in most, much less all, who are affected. At some point in the future such a test or marker may be discovered, but for now there are no mass applicable clinical, laboratory or pathological findings. Further, subjective complaints of patients may be overlooked, particularly if they vary from one person to the next. Thus clinico-pathologic studies are not likely to be sensitive to the early effects of low-level exposures, i.e., prior to end-organ damage.

What is needed is a sensitive tool that reliably detects symptoms of exposure to low levels of multiple chemicals in human beings taking into account individual variability, a tool that will allow us to ascertain cause-and-effect relationships between exposures and symptoms. The environmental unit is such a tool. It is the only one of the four tools listed above which may facilitate detection of disease at a sub-clinical level, in the pre-pathologic state. Potentially, it may be the most useful of the four approaches for studying man's response to environmental agents. For this reason, if for no other, the EPA and other governmental bodies concerned with regulating exposure to low levels of toxic environmental agents should take great interest in this approach. The individuals who might enter environmental units perhaps represent the most susceptible population. Their responses to chemical challenges while in a de-adapted state in an environmental unit would further our understanding of low level chemical sensitivity. Carefully designed and orchestrated studies with meticulous attention to the details of environmental control, as defined by Selner and the clinical ecologists who have operated such units, are essential to resolving these issues to the satisfaction of all.

B. Offending Substances

This section addresses the origins of multiple chemical sensitivity, i.e., the offending substances that may induce the disease, as well as those that trigger symptoms once the problem has begun. In the preceding section, adaptation was discussed in relation to several different materials including ozone, nitroglycerin, cotton dust, metal fumes, alcohol, tobacco smoke, etc. Adaptation to an enormous range of substances has been noted by clinical ecologists and their patients. These may be divided into five major subgroups:

(1) outdoor air pollutants
(2) indoor air pollutants, both domestic and workplace
(3) food contaminants and additives
(4) water contaminants and additives
(5) drugs and consumer products

In preparing this report we considered referencing representative articles from toxicology that would show that substances in the above categories may be toxic to animals or man. However, an encyclopedic listing would have little point. There is no argument that toxic substances in the environment have adverse health consequences. The question is do certain persons develop heightened reactivity to chemicals and foods? If so, why?

With the exception of certain IgE-mediated hypersensitivity reactions, studies of hyper-reactivity other than those done by the clinical ecologists are rare. Dr. John Selner, an allergist who advocates the use of an environmental unit for diagnosing certain patients, has attempted to perform studies of these hyper-reactive individuals. Regrettably, no studies of patients in an environmental unit were published by Selner either. The criticisms and "studies" to disprove this field have not involved independent investigations in which food and chemical challenges on patients in a de-adapted state were performed. Nor have any data been published to repudiate Randolph's observations on adaptation. Instead, criticisms have been aimed at the efficacy of treatments, e.g., provocation-neutralization, for chemically sensitive patients. These critiques of treatment modalities have been used as the basis for trying to disprove existence of the illness altogether.

Clinical ecologists, as well as some allergists [Selner 1988] with whom we spoke, invoke the concept of total body load or burden. To ecologists, this load is comprised of all of the incitants to which the body must respond (adapt) to maintain homeostasis. These may be chemical in nature, biological (pollens, molds, bacteria, viruses), physical (heat, cold, radiation, etc.), or psychological. Notwithstanding its utility as a theoretical construct to help "explain" why this disorder occurs in a given individual, total load per se is not measurable. However, part of it can be quantified. For example, Laseter et al measured levels of 16 chlorinated hydrocarbon pesticides in 200 chemically sensitive patients, 99% of whom had residues at or above 0.05 parts per million in their blood (reflecting even higher tissue levels) [Laseter 1983]. Volatile

organic hydrocarbons [Rea 1987] and aliphatic hydrocarbon solvents [Pan 1987] have also been measured in these patients, but their levels have not been compared with those of individuals not having such symptoms. Nevertheless, Rea and others feel that these substances are not normal constituents of the body and therefore they represent a substantial burden for the individual. However, even if there were no differences in levels between chemically sensitive patients and so-called "normals," these compounds still could be a source of their illness, since chemically sensitive patients may be a subgroup of the population that is more susceptible to the effects of these chemicals. In addition, what may be most relevant is what their exposure was in the past that may have caused them to become sensitized in the first place.

Some authors have attempted to distinguish between those chemical exposures associated with the onset of multiple chemical sensitivity syndrome and those which are associated with recurrence of symptoms, i.e., act as triggers once the syndrome has developed [Cone 1987]. Cone et al reported that among workers they studied with multiple chemical sensitivities, eleven reported that solvent exposures of various types had caused their problem; three pointed to pesticide exposures; one, hydrogen sulfide; one, copy machines; one, new materials including carpets. Once the syndrome had developed, triggers for recurrence of symptoms in these same patients were far more diverse and included such common exposures as tobacco smoke, perfume, scented soap, car exhaust, copiers, gas stoves, tar, smog, newspapers, new clothing in stores, leather, printed books, office buildings and glues.

In Terr's review of 50 cases seen by clinical ecologists, 43 of whom were referred to him by workers' compensation carriers for independent evaluation, the patients also attributed their illness to a wide array of exposures [Terr 1986]: sixteen complained of acute exposure to a chemical, three to pesticides, two to phenol; while thirty-four patients felt their illness resulted from chronic exposures, six from unspecified chemicals in their homes, four from office machines, three from organic solvents, three from smoke, three from foods, two from formaldehyde, two from the hospital environment, two from airplanes [Terr 1986]. These reports reflect fairly well the kinds of exposures that clinical ecologists allege precede their patients' illness.

Realizing that certain exposures may cause multiple chemical sensitivities, while others may simply trigger symptoms once the syndrome has developed, we next discuss in more detail the range and nature of exposures that are thought to contribute to this problem, exploring the five subgroups of exposures mentioned at the beginning of this section.

Health effects data on chemicals are notoriously inadequate. A 1984 study by the National Research Council attempted to assess the testing needs for various industrial and consumer chemicals [National Research Council 1984]. Figure 10 shows existing needs for health hazard assessment and toxicity data. No toxicity data or minimal data are available for 66% of pesticides and their supposed "inert" ingredients; 84% of cosmetic ingredients; 64% of drugs; 81% of food additives; and 88-90% of chemicals in commerce.

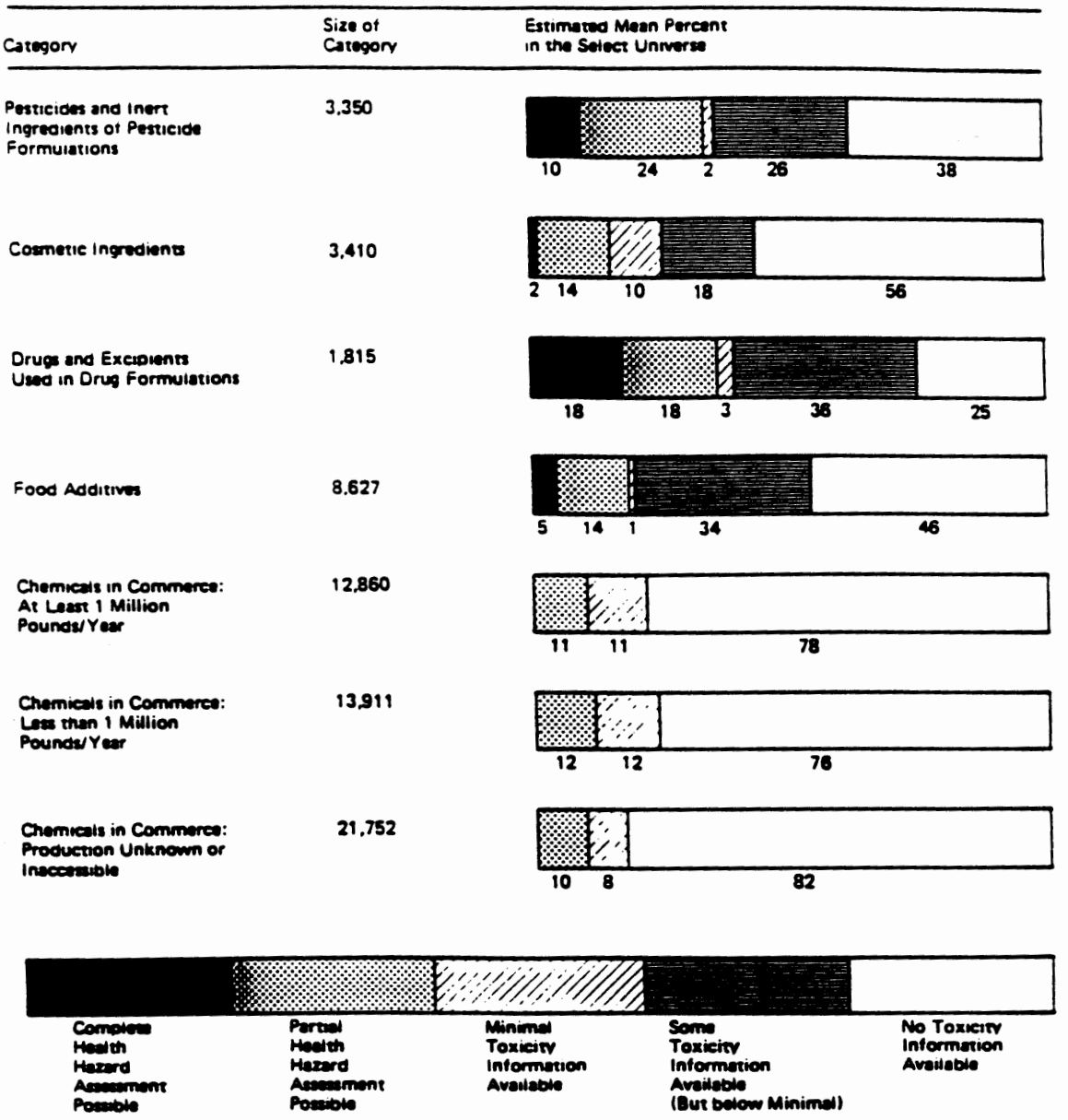

Figure 10: Ability to conduct health-hazard assessment of substances in seven catagories of a select universe of chemicals.
Source: National Research Council

Thus, scientific data concerning health effects of the vast majority of chemicals is woefully lacking. It is conceivable that chemically sensitive patients may fill in the gaps long before toxicologists do.

1. Outdoor Air Pollutants

Among the most hazardous exposures for patients seem to be pesticides either sprayed outdoors or indoors. Alone, pesticides have accounted for some of the most advanced and persistent cases of chemical sensitivity known to clinical ecologists. As early as 1966, occupational health practitioners observed that certain persons who had "recovered" from acute organophosphate pesticide poisoning experienced protracted symptoms of nausea, headache, irritability, insomnia, inability to concentrate, blurred vision or shakiness [Tabershaw 1966]. Twenty out of 114 individuals stated they could no longer tolerate smelling or contact with pesticides. Depression and schizophrenia occurs in others [Gershon 1961]. Neuropsychiatric, cardiopulmonary, and gastrointestinal symptoms may persist long after exposure to organophosphate insecticides [Namba 1971] which are widely used by exterminators indoors and out of doors. Other outdoor exposures presenting problems for the chemically susceptible patient include vapors from solvents and fuels, combustion products, tar fumes, paint vapors, diesel and auto exhaust and industrial air pollution [Randolph 1962].

The adverse effects of air pollution upon individuals with respiratory or cardiac compromise are widely acknowledged. Less well known, but increasingly studied, have been associations between outdoor air pollutant levels and psychiatric emergency-room visits [Briere 1983; Strahilevitz 1979]; psychiatric hospital admissions [Strahilevitz 1979]; family disturbances [Rotton 1985]; and anxiety symptoms [Evans 1988].

Randolph described a woman who became ill each time she journeyed through the industrial pollution of northeastern Indiana [Randolph 1987, 73-76]. Other patients note difficulty in any large metropolis, in the vicinity of airports, at bus or train stations or in heavy traffic.

Diesel exhaust is a particular problem for many patients. In an EPA review of the toxicology of diesel exhaust, Nelson projected, "I think we can conclude quite straightforwardly that a major increase in the Diesel fleet is not going to produce a disastrous epidemic of lung cancer," but "risk assessment should be the ultimate goal and should be given the highest priority" [Nelson 1982]. Many chemically sensitive patients experience severe symptoms with exposure to diesel exhaust. Interestingly, a Japanese study suggests that the striking increase in allergic rhinitis triggered by pollens which has occurred in that country over the past thirty years may be in part the result of lenient regulation of diesel exhaust and increased numbers of diesel vehicles [Muranaka 1986]. The authors note that the Japanese cedar, a tree indigenous to Japan for at least 1,000,000 years, was never known to cause allergic rhinitis until 1964; and that before 1950 allergic rhinitis was virtually unknown in their

country, although even then it had been recognized among Japanese living in the United States. Muranaka points to diesel exhaust as a possible cause for Japan's increasing allergic rhinitis.

As will be discussed in the following section, indoor air pollution rather than outdoor air pollution accounts for the greatest number and most intense exposures [Nero 1988]. There are two important reasons for this: First, most people spend the majority of their day indoors, either at work or home; second, the levels of exposure to many contaminants, particularly volatile organic compounds (many of which are uncharacterized and whose health effects are unknown) are much higher indoors than out-of-doors.

2. Indoor Air Pollutants, Domestic and Workplace

The scope of indoor air pollutants has been reviewed by others [Spengler 1983; Nero 1988]. The range of indoor air pollutants affecting industrial workers is enormous. Seemingly, almost any process involving chemicals appears to have the potential for initiating chemical hyper-reactivity via long- or short-term exposure. Two general types of exposures seem particularly apt to initiate hypersusceptibility:

(1) A massive, overwhelming exposure, such as a chemical spill, a fire involving synthetic materials, pesticide spraying or working with chemicals in a confined, unventilated space;

(2) Repeated, low-level exposure to a complex array of synthetic organic compounds, as occurs with combustion products (e.g., diesel), "tight" buildings, soldering, etc. [Miller 1979].

At home, troublesome exposures for the chemically sensitive patient include the gas stove, one of the most commonly identified triggers of symptoms in these patients; combustion products from gas- or oil-fired space heaters, water heaters, and central air heating systems; sponge rubber bedding, padding, and upholstery; plastics (especially pliable odorous plastics, e.g., shower curtains) insecticides; perfumes; paints and decorating materials; fireplaces; cleaning agents; mothballs; cedar closets; newsprint and other printed materials; fabrics in clothing, bedding, and window coverings, especially synthetics or coated fabrics; particle board; gasoline vapors from attached garages; and carpeting and carpet padding. Several guides for constructing homes from "safer" materials that are less toxic and/or do not offgas have been written [Rousseau 1987, Zamm 1980]. Urea formaldehyde foam insulation which may have provoked this illness in many in the past has ceased being used by insulators following a flurry of successful lawsuits. Mobile homes and automobile interiors present their own special problems. Indoor air pollutants in other settings may present problems: shopping malls; perfume counters; detergent and insecticide aisles; fabric stores; dry cleaners; deodorizers in public restrooms; tobacco smoke; incense; sterno used in buffets; gas cooking combustion products in restaurants; and perfume, cologne, or

mothball odors on garments worn in theaters and churches commonly cause difficulty for these patients. "Odors" of virtually any description may provoke symptoms; the presence of an odor implies that the substance in question has a vapor pressure and that molecules of it are present in the air. The subject of odors and their role in this syndrome is discussed in Section VA.

An historical note: Randolph first discussed the topic of indoor air pollution in a series of articles published in 1954 and subsequently in a book entitled Human Ecology and Susceptibility to the Chemical Environment in 1962. That same year, President Kennedy called the first national conference on air pollution in Washington, D.C. It was a three-day program with only an hour and a half at the end for open discussion. During the discussion, Randolph remarked that in three days of presentations, not a single reference had been made to indoor air pollution. In his clinical experience, he said, indoor air pollution was 8 to 10 times more important as a source of illness in susceptible individuals than outdoor air pollution. While outdoor air pollution tended to be intermittent and variable, indoor air pollution was much more constant. Further, individuals spend the majority of their day indoors. He also noted that over 800 gas stoves had been removed from the homes of his highly susceptible patients.

Of interest is the fact that 20 years later, pollution from the same sources Randolph had identified as triggers of his patients' symptoms was documented by using advanced and sensitive analytical techniques, e.g., gas chromatography with mass spectrophotometry, not available at the time of Randolph's original writings. Between 1979 and 1985, the EPA undertook an extensive study of exposures to volatile organic compounds of four hundred residents in three states, including New Jersey [Wallace 1987]. The TEAM study (Total Exposure Assessment Methodology) employed state-of-the-art monitoring and analytical methods. Each subject wore a personal air sampler for twenty-four hours and provided a breath sample at the end of the day. Personal exposures were consistently greater than outdoor levels, sometimes by factors of ten or more (closely approximating Randolph's estimates 20 years earlier), implying important indoor sources of exposure. Smoking, visiting the dry cleaner or gas station and certain occupations resulted in very elevated exposures. Breath levels were 30-40% of personal air concentrations for 9 of 11 compounds, but ranged as high as 75-80% for benzene (from gasoline) and 90% for tetrachloroethylene [Wallace 1985b]. Summarizing data from nine separate studies involving more than 1000 homes, Wallace reported that there was agreement on these points:

1) "Essentially every one of the 40 or so organics studied has higher indoor levels than outdoor.

2) Sources are numerous, including building materials, furnishings, dry-cleaned clothes, cigarettes, gasoline, cleansers, moth crystals, hot showers, printed material, etc.

3) Ranges of concentrations are great, often 2 or more orders of magnitude." [Wallace 1985b]

Clearly, exposures in most indoor situations occur at levels well below current OSHA or EPA standards. At a given moment, several hundred different chemicals may be present in air samples from a home or office. One question that arises is whether the summation of all of these chemicals' effects could be responsible for symptoms even though no single constituent accounts for them. To this end, Molhave of Denmark exposed 62 individuals to a mixture of 22 volatile organic compounds that commonly occur as indoor air pollutants [Molhave 1986]. Three concentrations of total pollutants were used: 0 mg/m^3 (control), 5 mg/m^3 and 25 mg/m^3 of the same mixture of 22 compounds. Using "healthy" subjects who had previously complained about symptoms of sick building syndrome, Molhave exposed them to each concentration for 2.75 hour periods in a double-blind, placebo-controlled design. As the air concentration increased, complaints of nasal and throat irritation and inability to concentrate, measured by digit span memory performance, rose. Thus, as the dose increased, these more "susceptible" individuals who otherwise appeared healthy were significantly affected by the indoor air pollutants, to the point of having difficulty with tasks requiring concentration.

Other Scandinavian researchers have found total volatile organic compound concentrations in homes with complaints by occupants to average 1.3 mg/m^3 (range 0.092 to 13 mg/m^3) while the concentrations in houses where there were no complaints averaged 0.36 mg/m^3 (range 0.02 to 1.7 mg/m^3) [Molhave 1986/1987]. Thus, levels of volatile organic compounds were generally higher in problem houses.

Turning to the white-collar work environment, Robertson et al compared health problems in two office buildings, one fully air-conditioned and the other naturally ventilated. Sickness was significantly increased in the air-conditioned building versus the naturally ventilated building: rhinitis (28% versus 5%), nasal blockage and dry throat (35% versus 9%), lethargy (36% versus 13%) and headache (31% versus 15%) [Robertson 1985]. Temperature, humidity, air velocity, etc., did not differ between the two buildings, suggesting that the sickness was caused by indoor air pollutants. Similarly, Finnegan and co-workers found significant excesses of eye, nose and mucous membrane symptoms as well as lethargy, dry skin and headaches among workers in air-conditioned versus naturally ventilated offices [Finnegan 1984].

An unanticipated and unwelcome opportunity for the EPA to study, first-hand, the effects of indoor air pollution arose when new carpeting was installed in the agency's headquarters in Washington, D.C., in 1987-88 [Hirzy 1989a, 1989c]. An estimated 124 of 2000 employees exposed to volatile off-gassing from the carpet became ill, exhibiting symptoms ranging from eye, nose, and throat irritation and breathing problems to nausea, headache, dizziness, difficulty in thinking, fatigue, and increased susceptibility to many exposures formerly tolerated. At least two employees quit their jobs as a result of illness. Seventeen were unable to work in their assigned spaces. Some now work at home or in other locations. Eight report new sensitivities

to common substances including perfumes, auto exhaust, and tobacco smoke. Symptoms of the twenty or so most severely affected individuals appear identical to those of patients seen by clinical ecologists. Agency scientists analyzed air samples and feel the culprit may be 4-phenylcyclohexene (4-PC) which is used to bind carpet fabric to its backing. Estimates of the exposures that initiated illness in the susceptible subgroup range from 1 to 10 parts per billion of 4-PC. These same persons, now "sensitized," experience symptoms upon re-exposure to less than one part per billion of the substance; the symptoms include respiratory difficulty, dizziness, "spacey" feelings, and general malaise.

These are compelling data from the federal agency charged with protection of the environment. This lends further credence to Randolph's and other clinical ecologists' observations with respect to: (1) diverse symptoms occurring in different individuals even with the same exposure, (2) "spreading" of sensitivities to other low-level exposures which formerly had been tolerated, and (3) adaptation--the less severely affected employees noted improvement in symptoms while away from work with marked increase upon return and gradual subsidence during the work week as tolerance developed [Hirzy 1989b].

3. Foods, Food Additives and Contaminants

Rea estimates that food sensitivity occurs in about 80% of his patients with chemical sensitivities [Rea 1988a]. Ecologists observe that excessive chemical exposure may result in loss of tolerance to foods, sometimes every food in the diet, and that removing the individual from such exposures and rotating foods so that no food is eaten more that once every four days may restore dietary tolerance. Pesticide residues, can linings (the gold-brown lining of cans may contain a phenolic resin), fumigants, fungicides, sulfur treatment, artificial colors, sweeteners, preservatives, ripening procedures (e.g., ethylene gas), protective waxes, and packaging materials, especially plastics, may trigger symptoms in patients. When patients are challenged with foods in an environmental unit, at first they are given chemically less contaminated foods, i.e., organic meats and produce wherever possible. Once a variety of "safe" foods have been determined and prior to discharge from the unit, patients may be given several consecutive meals using commercial preparations of their "safe" foods. These might include commercial apples that have been sprayed (the reader is reminded of the current concern over alar spraying of apples with alar causing possible long-range effects in children who consume these apples or apple juice), canned foods, non-organic meats, etc. After two days of such feedings, many patients reportedly experience fatigue, headache, myalgia, arthralgia, arthritis, depression and other muscular, skeletal, and/or neurological symptoms [Randolph 1987].

4. Water Contaminants and Additives

According to Rea, as many as 90% of his patients with chemical sensitivities may have reactions to contaminants in drinking water [Rea 1988a]. While fasting in an environmental unit, patients test waters from a variety of sources including tap water, specially distilled or filtered water, and various spring or well waters until they find one that does not evoke symptoms.

Chemical contamination of ground water is a growing national concern. Aldicarb, a carbamate insecticide-nematocide used extensively since the 1960's was first noted as a ground water contaminant in the late 1970's when over 1100 wells in New York's Suffolk County, a potato farming region on Long Island, tested positive for aldicarb (levels greater than seven parts per billion). Since that time, aldicarb has been found in ground waters of Maine, Florida, California, Arizona, North Carolina, Virginia, and Wisconsin. In Wisconsin, 23 apparently healthy women who consumed ground water with detectable aldicarb were found to have altered T-cell subsets with a decreased T_4:T_8 ratio of 1.88 versus 2.54 in an unexposed control group ($p<0.05$) [Fiore 1986]. Unlike AIDS, where the T_4:T_8 ratio is decreased primarily because T_4 (helper) cells are destroyed by the virus, in these women there was in increase in T_8 (suppressor) cells. In addition, lymphocyte proliferation in response to Candida allergen was increased ($p<0.02$) versus controls. Likewise, among residents of Woburn, Massachusetts who drank water that had been contaminated with industrial solvents excess leukemias (12 versus 5.3 expected); immunological abnormalities including decreased T-cell ratios ($p<0.01$); increased autoantibodies and infections; and neurological, cardiac, and skin abnormalities were noted [Byers 1988] (see also Section VA).

Ingestion is not the sole route of exposure to contaminants in water. Brown et al reported that skin absorption, e.g., from bathing or showering, may be a significant portal of entry for water contaminants accounting for 29% to 91% (average 64%) of the total daily dose of these substances [Brown 1984]. Aside from skin contact, showering volatilizes contaminants in water leading to inhalation of chlorine, chloroform and organics compounds [Bailey 1987; Foster 1987]. Water contaminated with organic material, when it is subsequently chlorinated, will contain chlorinated hydrocarbons that are potentially carcinogenic. Interestingly, chemically sensitive individuals frequently note symptoms while bathing or showering and some chlaim they must use specially filtered water or at least water treated to remove the chlorine.

5. Drugs and Consumer Products

It is widely recognized among physicians that persons who have an adverse reaction to one drug are more likely to react to other drugs. Sullivan, an allergist, recently reported that individuals who experienced an adverse reaction to penicillin

are much more likely to react adversely to other drugs, in particular antibiotics. Interestingly, he calls this phenomenon, which occurs in a very small percentage of the population, the "multiple drug allergy syndrome." The mechanism is unclear, but may be related to faulty regulation of anti-hapten immune responses, he postulates [Sullivan 1989]. Meggs compiled a list of symptoms that have been reported for seven well-known pharmaceuticals (indomethacin, propranolol, azatadine, pseudoephedrine, captopril, diazepam, and reserpine) [Meggs 1989a]; these symptoms reproduced about 80% of the symptoms/complaints Terr reported in patients exposed to various organic chemicals. Meggs comments, "Perhaps there is a similarity between adverse reactions to pharmaceuticals and volatile organic compounds found in the workplace. Again we are dealing with low molecular weight carbon-based compounds of similar structure in the two cases" [Meggs 1989a].

Randolph surveyed a series of 80 and another series of 250 of his chemically sensitive patients who had "known" reactions to some facet of their chemical environment and found an extraordinarily high percentage had reacted adversely to one or more medications [Randolph 1962, 85-87]. One quarter to one half claimed to have reacted to each of these drugs: Aspirin, barbiturates, and sulfonamides. According to Randolph, because of this proneness to drug reactions and because many physicians do not understand this problem, many individuals with chemical sensitivities are reluctant to seek health care. Thus in some cases there appears to be a significant overlap between individuals who react badly to medications and chemically sensitive patients. It would be worth investigating whether a disproportionate number of the idiosyncratic reactions listed in the Physician's Desk Reference occur in the same subgroup of patients. Schottenfeld, a psychiatrist, confirms that many individuals with multiple chemical sensitivities appear unusually sensitive to the anticholinergic and sedative effects of tricyclic antidepressants [Schottenfeld 1987].

Drugs, of course, contain much more than an active ingredient(s). They also contain excipients (e.g., cornstarch or lactose in tablets), diluents, coloring agents, flavorings, various coatings, phenol or other preservatives (as in allergy shots, which typically contain 0.5% phenol). Mineral oils, petroleum jelly, ointment, lotions, laxatives, synthetic vitamins, and adhesive tape may cause problems for many patients. Virtually all cosmetics, scented soaps, shampoos, hand lotions, personal hygiene products, perfumes, colognes, deodorants, hair sprays, hair dyes, mouthwashes, denture adhesives, bath salts or oils have been reported to provoke reactions in these patients.

In addition, permanent press finishes (especially during ironing); synthetic textiles; clothes that have been dry-cleaned; residues of detergents; fabric softeners; electric blankets (the plastic coatings over the wires off-gas when heated); felt-tip pens; odorous books, magazines and newsprint; polishes, cleaners, and bleaches; and chlorinated swimming pools or even bath or shower water have also been associated with intolerance [Randolph 1962, 112-114].

The very ill patient may be sensitive to most if not all of these substances and products and has difficulty avoiding or finding suitable substitutes. Mail order services often begun by patients have developed to help sensitive individuals find products better tolerated. Exposures may be very subtle. For example, individuals may find themselves irritable or anxious when talking on the telephone, but if they substitute a Bakelite phone for their new colored plastic one or use a speaker phone instead, their problem resolves [Randolph 1962]. Clothing that was stored in particle board drawers may emit formaldehyde, triggering symptoms. Synthetic fabrics have been implicated in elevated blood pressure, increased heart rate, arrhythmias and angina [Seyal 1986a-d]. Acrylic dentures may provoke headache, joint pain, fatigue and rashes [Kroker 1982].

The process of discovering the limits of one's tolerance may be long and tedious, with many setbacks. The setbacks can be so painful and disabling that patients go to great lengths to educate themselves about chemicals and avoid them. Very sensitive patients may react adversely to dental materials; medical implants or prostheses; local anesthetics; plasticizers leaching from plastic IV or oxygen lines; lubricating jelly applied during an examination; or evaporating alcohol on the skin when blood is drawn. Such patients view any encounter with an unknowing or disbelieving dentist or physician with great trepidation. If surgery is planned, they may inquire what intravenous solutions will be used (D_5 is five per cent dextrose and thus contains corn sugar; corn is the most common food that provokes symptoms in these patients [Randolph 1980, 109]), what anesthetic drugs will be used, etc., so as to prepare themselves and their doctors for any adverse reaction and attempt to avert it. Many practitioners find such inquiry intimidating or view the patient as hypochondriacal, when in fact the patient, in need of an operation or special procedure, only wishes to avoid an adverse reaction. Practitioners need to understand these patients' concerns and realize that the patients' fears may be well-founded in prior experiences with very painful or embarrassing reactions. When they must place themselves in the hands of doctors, chemically sensitive patients feel a lack of control and a vulnerability most would not understand.

C. Health Effects

According to the clinical ecologist, the symptoms and diseases caused by food and chemical exposures involve any and every system of the body and are so diverse that many traditional practitioners find them unbelievable. Some of the physicians we interviewed recalled being told as medical students that the more symptoms a patient complained of, the less validity there was to any of them. Clearly, such a belief by physicians could pose an obstacle when the average patient with food and chemical sensitivities who enters an environmental unit has five symptoms, many of them neurological [Johnson 1989].

To many non-ecologists, a troublesome aspect of the provocative food and chemical challenges performed by clinical ecologists has been the differences seen in symptoms on challenge versus those which were part of the patient's chief complaint at presentation. In his critique of fifty patients who previously had been seen by clinical ecologists, Terr, an allergist, noted that thirty of the patients (60%) developed one or more new symptoms during their diagnostic and therapeutic experience with the clinical ecologist [Terr 1986]. Of these the most frequent were headache (30%), fatigue (23%), confusion or loss of memory (20%), swelling (20%), dizziness (17%), depression (17%), nausea (17%) and rash, drowsiness, anxiety and abdominal pain (13%). It must be remembered that forty-three of Terr's fifty patients were referred for workers' compensation evaluation and thus represent the "worst" cases. In comparison, less than 5% of the patients seen by Randolph and about 20% of those seen by Rea (who sees sicker patients referred by other ecologists) apply for disability. The frequent emergence of "new" symptoms during de-adaptation and re-exposure is well known to clinical ecologists. Unfortunately, Terr does not offer any of the patients' own commentary about their illness. Sixty-two percent, however, had a long history of multiple symptoms involving many systems and parts of the body, and had been examined, tested and treated unsuccessfully for years by many physicians prior to seeing a clinical ecologist. Perhaps some of their "new" symptoms did occur in the past but were forgotten since they were transient in nature. Perhaps adaptation occurred, "masking" many of the symptoms. To the clinical ecologist, patients with very advanced environmental illness are manifesting the most extreme, overlapping, stimulatory and withdrawal reactions to multiple substances. Chronic disability may ensue. However, if the patient is withdrawn from inciting chemical exposures and placed on a "safe" diet as described in Section IV A2, one may be able to reverse the experience and begin to associate cause and effect. Specific symptoms can then be attributed to identifiable chemicals or foods in a reproducible way. Following de-adaptation, symptoms that have not been experienced for decades may manifest (i.e., there is "unmasking"). As long as multiple exposures causing multiple effects are overlapping, symptoms are masked and the person may instead experience chronic disability or end organ failure of some type.

It is important to differentiate the acute symptoms experienced by a patient when a clinical challenge is performed (see Table VI) from the chronic disease states that are purported to result from chronic exposure to incompatible foods and

Table VI

POSSIBLE ACUTE REACTIONS TO INCITANTS DURING PROVOCATION
[Rea 1984b]

Nasal:
Sneezing--urge to
Itching--rubbing
Obstruction
Discharge
Postnasal Drip
Sinus Discomfort
Stuffy Feeling

Throat, mouth:
Itching Sore--Tight--Swollen
Dysphagia, difficulty in swallowing--Choking
Weak Voice--hoarse
Salivation--mucus
Bad or metallic taste

Ears:
Itching
Full--blocked
Erythema of pinna (reddening)
Tinnitus--ringing in ears
Earache
Hearing loss
Hyperacusis--abnormal sensitivity to sound

Lungs, Heart:
Blood Vessels
Coughing
Sneezing
Reduced air flow
Retracting--shortness of breath
Heavy--tight
Not enough air
Hyperventilation--rapid breathing
Chest pain
Tachycardia--rapid pulse
Palpitations--rapid, violent or throbbing pulses; extra or skipped beats
Blood vessels--spontaneous bruising and petechiae, cold sensitivity, swelling, acneform lesions

Table VI continued

Joints:
Ache-pain
Stiff
Swelling
Erythema-warmth-redness

Muscles:
Tight-Stiff
Ache-sore-pain
neck
upper, lower back
upper, lower extremities

Skin:
Itching local-general
Scratching
Moist-sweating
Flushing-hives
Pallor-white or ghostly

Eyes:
Itch-burn-pain
Lacrimation-tearing
Injected-light sensitive
Sensitivity shiners
Feel heavy

Vision:
Blurring
Acuity decreased
Spots-flashes
Darker-vision loss
Photophobia-brighter
Diplopia-double vision
Dyslexia-difficulty reading, transposition of letters; letters or words becoming small, or large; words moving around.

Cerebral--Head:
Headache, mild-moderate; Migraine
Ache-pressure: tight-explode
Throbbing - stabbing
Fainting
Depression
Mood swings
Hallucinations
Hyperactivity
Irritability
Fatigue
Apathy
Confusion
Lethargy
Blackouts
Insomnia
Somnolence

Genitourinary:
Voided--mild urge
Frequency--in voiding
Urgency--pressure
Dysuria--painful or difficult urination
Genital itch
Vaginal discharge
Yeast infection

Gastrointestinal (Gut):
Nausea
Belching
Full--bloated
Vomiting
Pressure--pain--cramps
Flatus--rumbling--gas
Diarrhea
Gall bladder symptoms
Hunger--thirst
Hyperacidity

chemicals. The latter, according to clinical ecologists, include a wide range of diseases or disorders. Traditional practitioners consider many of these disorders "idiopathic" or "essential" (as in "essential hypertension") or give them names that are descriptive, e.g., "asthma" or "urticaria," that are not revealing about possible causes. Clinical ecologists claim that many of these conditions are caused by environmental incitants (food or chemical).

The definitive test would be to place the patient in an environmental unit and having him fast. If symptoms which were chronically present and debilitating resolve, this suggests an environmental cause. "Proof" of environmental causation involves re-challenge with single foods and chemicals and noting effects. If an effect is reproducible, causation is inferred. Confidence regarding causation would be strengthened by double-blind placebo-controlled challenges.

In the pages that follow is an annotated bibliography for health effects felt by some to be related to foods and chemicals. Many, but not all, sources listed were written by clinical ecologists. For certain diseases, e.g., migraine and atopic dermatitis (eczema), there is growing acceptance among traditional practitioners as well that foods may play an important role in certain patients.

This bibliography is not intended to be encyclopedic. Rather it is an attempt to present the range and diversity of diseases for which environmental (food or chemical) origins have been proven or proposed. It is also designed to help the reader identify key articles on particular disorders since many of these articles have appeared in older or less widely circulated journals and would otherwise be difficult to locate.

The majority of the articles discuss foods, rather than chemicals, as potential factors in disease. Nevertheless, most of the diseases listed here have also been attributed to chemical exposures by some observers. Randolph's observations of patients worked up in an environmental unit are summarized in his books and papers and provide interesting anecdotal accounts of the role chemicals might play in particular conditions.

By presenting this material we are not affirming an environmental cause for these diseases, but hoping to alert the reader to that possibility and the need for evaluating such patients in an environmental unit when more traditional approaches have failed. What might seem obvious--that foods and chemicals are not significant factors in most of these disorders--could change if one were to eliminate masking and control for the effects of adaptation.

We cannot overemphasize the importance of not confusing recognizing the existence of a disease with knowing its cause. Terr in his reviews of ecology patients criticizes the ecologist for attributing illness in these patients to environmental factors where they clearly had other well-defined clinical diseases such as depression [Terr 1989a, 1986]. In a critique of Terr's most recent review of ecology patients [Terr

1989a], Dr. William Meggs, Assistant Professor of Medicine at East Carolina School of Medicine, asserts:

> "First, both Dr. Terr and the clinical ecologists consistently confuse diagnosis and etiology. Environmental illness, ecological illness, or similar terms should not be used as a diagnosis, which is the error of the clinical ecologists. Dr. Terr's error is to state that since a patient has another diagnosis, the diagnosis of environmental illness is wrong, and therefore there is no environmental cause of the illness.... In his methods section Dr. Terr does not discuss how he determined that the patients's symptoms were not triggered by environmental exposures. Many of the symptoms he lists in Table 4 of his article such as asthma, rhinitis, and dermatitis are known to have an environmental etiology in some patients, and generally accepted methods are available for verification.... Correctly diagnosing an autoimmune condition in a patient claiming environmental illness, rather then disproving an environmental etiology, should alert the physician to look for an environmental cause. The claim that psychiatric disorders can be triggered by chemical exposures is worthy of serious scientific study, particularly with increasing rates of depression.... Cases of depression related to exposure to furnace fumes were described by Randolph thirty years ago." [Meggs 1989b]

[See Randolph 1955 regarding furnace emissions causing depression.]

Thus while allergists accuse ecologists of over-zealously diagnosing environmental illness and overlooking other important medical conditions [Bardana 1989; Terr 1989a, 1986], some allergists may have wrongly assumed that just because a patient's condition has an accepted medical label that this somehow rules out an environmental etiology. Both approaches are in error. What is needed is a more thorough and more balanced approach. To achieve this, physicians need to be aware of the wide variety of medical conditions for which environmental (either food or chemical) etiologies are being considered. We have attempted to pull together some of the most pertinent articles in this annotated bibliography. They are arranged under the following headings:

1. Alcoholism, Drug and Food Abuse
2. Cardiac and Vascular Disease
3. Eye, Ear, Nose and Throat Disorders
4. Endocrine Disorders
5. Fatigue
6. Gastrointestinal Disorders
7. Gynecologic Disorders
8. Hematologic Abnormalities
9. Neurobehavioral and Psychiatric Manifestations
10. Neurological Disorders
11. Pulmonary Disorders

12. Renal and Urologic Disorders
13. Rheumatologic Disorders
14. Skin Diseases

1. Alcoholism, Drug and Food Abuse

Alcoholism - termed the "ultimate food addiction" by Randolph in the late 1940's [Randolph 1956; 1976c; 1980, 109-116]. Persons who drink heavily may be sensitive to the food from which the alcoholic beverage is derived. For example, bourbon drinkers may be sensitive to corn and may need to avoid all sources of corn in order to control their cravings [Randolph 1987, 40-47]. Individuals may first become aware of a food intolerance when they react adversely to a particular alcoholic beverage, e.g., vodka (potatoes), wine (grapes) or bourbon (corn). Alcohol is quickly absorbed so that the individual is more aware of his symptoms being associated with a particular alcoholic beverage than with the corresponding food. For example, a person who develops a headache only 3 minutes after drinking bourbon, might have a headache 10-12 minutes after eating corn sugar, 20-25 minutes after cornstarch and only a scratchy throat 2-3 hours after corn oil. The time for symptoms to manifest thus depends upon the rate of absorption. According to Randolph, the majority of alcoholics in this country are addicted to corn; if they manage to abstain from alcohol they often substitute corn sugar in the form of candy, ice cream, or some other corn-containing food [Randolph 1987, 184].

Obesity - "characteristically involves addiction to several foods" [Philpott 1976]. Insatiable hunger may emerge as a withdrawal symptom from certain foods or chemical exposures, making adherence to a weight reduction diet exceedingly difficult [Randolph 1956]. Diets structured around calorie restriction most often fail because foods that the dieter is addicted to and thus craves have not been eliminated. "Suffice it to say, briefly, that obesity and alcoholism are basically similar illnesses, one dealing with addicting foods in their edible form and the other in their potable form" [Randolph 1980, 100].

Tobacco Use [Philpott 1980] Philpott reported that 75% of schizophrenics he saw in his practice exhibited psychiatric symptoms when smoking cigarettes. Following a 2-3 week period of abstinence (de-adaptation), ten percent became psychotic upon re-exposure to tobacco smoke [Philpott 1980]. Many physicians recall with displeasure how smoky psychiatric ward lounges were when they rotated through psychiatry as students and recall being taught to allow a patient who seemed to be decompensating the opportunity to smoke a cigarette.

Tobacco belongs to the nightshade food family along with potato, tomato, eggplant and green pepper. Smokers, who are addicted to tobacco, may have sensitivities to these as well (paradoxically, sensitivity may result in

either a strong dislike for these foods or a craving for them, i.e., addiction) [Randolph 1987, 253].

2. Cardiac and Vascular Disease [Rea, 1981; 1987] Rea, a thoracic surgeon prior to his involvement with clinical ecology, reviews cardiovascular disease from the clinical ecologists' perspective.

Arrhythmias [see above; also Boxer 1976; Seyal 1986b, 1986d]

Vasculitis [see above]

Thrombophlebitis [see above]

Hypertension [Seyal 1986b; 1986c] Increased blood pressure, heart rate, and arrhythmias are attributed to the wearing of synthetic clothing versus cotton clothing by Seyal.

Angina and Myocardial Infarctions [see above; also Seyal 1987/1988; Kalsner 1984; Speizer 1975; Taylor 1970] Numerous studies outside of clinical ecology support the idea that environmental agents may trigger cardiac symptoms. Kalsner reported in Science that histamine levels are increased in coronary arteries of cardiac patients, suggesting that "an 'allergic' response as occurs in an antigen-antibody type reaction could induce a powerful contraction or spasm of a coronary vessel segment and precipitate a cardiac crisis such as angina or rhythm disruption" [Kalsner 1984]. It is widely recognized that nitroglycerin may provoke angina (referenced earlier in Section IV A) and that fluorocarbons in aerosol propellants may precipitate arrhythmias [Speizer 1975; Taylor 1970].

Edema and Fluid Retention Syndromes [see above]

3. Eye, Ear, Nose and Throat Disorders [Rea 1979] Ear, nose and throat symptoms secondary to environmental triggers may be a common early warning sign of environmental hyper-reactivity, with heightened awareness and intolerance of odors being one of the most common symptoms. Roughly 20% of ENT physicians practice allergy themselves and perhaps about one-third of these physicians are interested in chemical sensitivity. Some refer their patients with multi-system complaints to clinical ecologists.

Eye Disorders, e.g., conjunctivitis, eczema of the eyelids, blurring of vision, tearing, light sensitivity (photophobia) [Rapp 1986b; also see indices of Randolph 1980 and Rapp 1986 for individual cases].

Laryngeal Edema [see above; also LaMarte 1988] Using videoendoscopy of the larynx, LaMarte and coworkers documented laryngeal edema in a patient exposed to the alkylphenol novolac resin used in making carbonless carbon

paper. Concomitantly, plasma histamine levels rose six-fold higher than pre-challenge. Similarly Selner [1985b] showed spasm of the pharyngeal constrictor muscles in a woman exposed to copy machine "fumes" when challenged in a blinded fashion with sham challenges as controls.

Meniere's Disease [see above]

Otitis Media [see above; also Pelikan 1987; Shambaugh 1983; Boris 1985; Bernstein 1988] Bernstein reported 2-3 fold more serum IgE directed against milk, eggs, and wheat among a group of 10 otitis prone children (six or more episodes in first two years of life) compared to 18 controls (less than four episodes in the first two years).

Rhinitis, "Frequent Colds," Chronic Nasal Obstruction [see above; also Pelikan 1987]

Salivary Gland Malfunction [see above]

Sinusitis [see above]

Vertigo, Hearing Loss, Tinnitus, Pressure in Ear [see above; also Odkvist 1985; Powers 1976]

4. **Endocrine Disorders** [Saifer 1987]

Thyroid Dysfunction Gaitan hypothesizes that organic and microbial water pollutants may be responsible for an increased incidence of goiter and auto-immune thyroiditis in certain regions [Gaitan 1985]. Polychlorinated biphenyls (PCB's) and polybrominated biphenyls (PBB's) may interfere with thyroid hormone secretion [Bastomsky 1985/1986]. Eleven percent of workers at a plant manufacturing PBB's were hypothyroid and showed increased titers of thyroid anti-microsomal antibodies, perhaps resulting from a PBB-induced auto-immune response [Bahn 1980].

Premenstrual Syndrome [Rea 1988b; Mabray 1982; 1982/1983]

5. **Fatigue** [Randolph 1980, 138-146; 1945; 1947] Randolph's writings on this subject extending back to the 1940's suggest that fatigue syndrome, an illness currently the subject of great discussion among physicians, might be investigated on this basis (environmental unit, fasting). Indeed, Randolph reported seeing many atypical lymphocytes in the peripheral blood smears of chronic allergic patients, resembling mononucleosis, which has been implicated by some in chronic fatigue syndrome [Randolph 1944]. Fatigue is reportedly one of the most common manifestations of food and chemical sensitivity and

resolves with avoidance of incriminated foods and chemicals. Drowsiness following a meal is said to be a common sign of food sensitivity.

6. **Gastrointestinal Disorders** Certain digestive tract disorders have been clearly linked to foods, e.g. gluten sensitive enteropathy is associated with wheat consumption, but traditional gastroenterologists doubt or remain uncertain about the role of foods in many other conditions. Note: The following papers concern food as triggers of gastrointestinal disorders, however, chemical exposures are also reported [see Randolph's books] to result in increased food intolerance, bloating, heartburn and other gastrointestinal manifestations.

Oral Manifestations including aphthous ulcers [Challacombe 1987; Ford 1987; Hindle 1986]

Celiac Disease (gluten sensitive enteropathy) [Mike, 1987]

Enterocolitis in Infants [Van Sickle 1985] Lymphocytes from infants with milk or soy intolerance (demonstrated by oral food challenge) had an augmented response to mitogen stimulation when cultured with soy protein or milk protein.

Eosinophilic Gastroenteritis [Trounce 1985]

Inflammatory Bowel Disease [Shorter 1987]

Crohn's Disease [see above]

Chronic Ulcerative Colitis [see above; also Rowe 1949; McEwen 1987] Food sensitivity was proposed as the principal cause of ulcerative colitis by Rowe in 1942.

Irritable Bowel Syndrome [Jones 1982, 1987] Jones et al found that specific foods induced symptoms of irritable bowel syndrome in 14 of 21 patients; double-blind food challenges with six patients confirmed food intolerance.

7. **Gynecologic Disorders** [Mabray, 1982; 1982/1983; 1983]

Premenstrual Syndrome (PMS) [see above; also Rea 1988b]

Infertility [see above]

Dysmenorrhea [see above]

Fibrocystic Breast Disease (breast tenderness) [see above; also Russell 1989; Hindi-Alexander 1985; Boyle 1984; Levinson 1986; Lubin 1985; Jacobson 1986]

Russell demonstrated that breast pain can be mitigated by eliminating caffeine from the diet. A study published in the allergists' Journal of Allergy and Clinical Immunology found that the total methyl xanthine content in the diet (including tea; coffee; chocolate; colas; and theophylline, which is used to treat asthma) was predictive of fibrocystic breast disease severity [Hindi-Alexander 1985]. Other papers confirm this relationship [Boyle 1984] or dispute it [Levinson 1986; Lubin 1985]. Jacobson discussed the limitation of case controlled studies of fibrocystic breast disease: such studies can easily miss an association if not all cases have the same disease or if all individuals are not equally sensitive to methyl xanthines [Jacobson 1986]. Interestingly, Jacobson felt further case controlled studies would be futile and suggested instead double-blind controlled challenges to resolve the debate once and for all.

8. **Hematologic Abnormalities**

Anemia [Heiner 1962] IgE is clearly involved in Heiner's syndrome in which milk consumption results in anemia, poor weight gain, gastro-intestinal symptoms, severe, recurrent lung disease, and upper respiratory tract symptoms; other concomitant mechanisms play a role in this syndrome.

Thrombocytopenia [Caffrey 1981]

9. **Neurobehavioral and Psychiatric Manifestations** [Randolph 1980; Pearson 1987; King 1981; Bell 1982a, 1982b, 1987a, 1987b] Randolph describes the stimulatory and withdrawal effects of environmental incitants (see Section IV A) and their psychiatric correlates, ranging from hyperactivity (+ +), autism, anxiety, mania, panic attacks and seizures at the furthest extreme (+ + + + +), to withdrawal levels, including "brain fag," i.e., impaired thinking ability (---), and severe depression (---, ----). King performed double blind sublingual testing on 30 patients complaining of at least one psychological symptom using conventional food allergic extracts as well as tobacco smoke extract and was able to provoke cognitive-emotional symptoms more frequently using these incitants than placebo ($P = 0.001$).

Affective Disorders (Depression, mania, etc.) [Bell 1987a; Randolph 1980, 147-155]

Anxiety and Somatoform Disorder [Bell 1987a] Note: Bell cautions, "...psychological diagnoses such as somatization disorder are always diagnoses of exclusion of organic factors. If a double-blind study is inadequately designed, researchers might miss a true biological effect and mistakenly conclude a psychogenic basis for the presenting complaints. In addition, the finding of psychological factors does not rule out biological components to a phenomenon."

Sexual Dysfunction [Randolph 1976f]

Eating Disorders [Bell 1987a]

Hyperkinesis [Egger 1987b; Rapp 1986]

Schizophrenia [Bell 1987a; Philpott 1976b, 16; King 1985] See "Tobacco Use" in this section. Philpott wrote that the schizophrenic patient usually is sensitive to a wide assortment of substances. Foods most likely to provoke reactions included wheat (64%), corn (51%), and milk (50%). Tobacco and coffee also produced symptoms frequently. King reviewed studies of wheat gluten as a factor in schizophrenia and reported that the studies with more adequate statistical power were positive and suggest that wheat gluten may provoke schizophrenic symptoms.

10. Neurological Disorders

Headaches of almost any description (tension, migraine, "sinus," etc.) are considered by ecologists to be common manifestations of food and chemical intolerance [Randolph, 1979]. Randolph cautions that "headache diets" most often do not relieve the patient's symptoms either because they fail to exclude certain key foods or important chemical exposures are not avoided. No single diet works for all patients; foods must be tested for each individual. Frequently patients note that a particular food relieves their headache yet are unaware that the same food may also be the cause. [Randolph 1980, 123-128]

Migraine [see below; also Monro 1987; Egger 1983, 1987a, 1989; Mansfield 1985]

Seizure Disorders [Bell 1987a; Egger 1989] Egger found improvement in 40 of 45 children with epilepsy and migraine placed on an oligo-antigenic elimination diet; complete control of seizures was achieved with 25 patients; double-blind, placebo-controlled challenges conducted in eight patients provoked seizures. None of 18 patients with epilepsy alone improved. Alternation between seizures (+ + + +) and headache (--) (see Table IV) in some individuals is recognized by neurologists but the mechanism is not known. Randolph's description of the levels of addiction provides a possible context for understanding this phenomenon.

Sleep Disorders [Bell 1987a] Sleep apnea, hypersomnia, narcolepsy, and restless legs syndrome are discussed.

11. Pulmonary Disorders

Asthma [Wraith 1987; Shim 1986; Gerdes 1980; Stankus 1988; Hoj 1981] Bronchospasm in certain workers exposed to toluene di-isocyanate and certain other industrial chemicals is undisputed among medical practitioners, however, such responses to tobacco smoke or perfume are often questioned or dismissed as irritant reactions. Shim, a pulmonary specialist, challenged four asthmatics with cologne for 10 minutes; their pulmonary function tests (FEV_1) dropped 18 to 58% below baseline. Fifty-seven of 60 asthmatics he surveyed complained of respiratory symptoms with exposure to common "odors": insecticide (85%); household cleaners (78%); perfume/cologne (72%); cigarette smoke (75%); fresh paint (73%); auto exhaust fumes (60%); and cooking smells (37%).

Gerdes and Selner studied a 35 year old steroid dependent asthmatic who complained of worsening bronchospasm after eating corn. Double-blind challenges with D_5NS (normal saline with 5% dextrose, a corn derived sugar) and plain normal saline showed a reproducible decrement in pulmonary function after dextrose only. Stankus, Salvaggio, et al studied 21 asthmatics (19 atopic) who complained of cough, shortness of breath and chest tightness with exposure to cigarette smoke. Seven of 21 experienced significant, reproducible reductions in their ability to perform pulmonary function tests (more than 20% decrease in FEV_1) when exposed to cigarette smoke for two hours. The gradual declines in FEV_1 that occurred were unlike the usual early or late responses induced by classic allergen inhalation testing and there was no association with serum IgE antibodies or skin tests to tobacco leaf extract. Accordingly, the authors comment that the mechanism of bronchospasm from cigarette smoke is unclear. Of interest is their finding that the other 14 asthmatics who claimed they were sensitive to cigarette smoke did not experience bronchospasm with challenge testing. It is conceivable that these individuals might show positive challenges if the testing were done while in the de-adapted state, i.e., after an appropriate interval (e.g., 4 to 7 days, no longer and no shorter) away from cigarette smoke. Some of these individuals may have avoided smoke for weeks or longer and thus have lost their sensitivity.

Pneumonitis [Heiner 1962] (See "Anemia")

12. Renal and Urologic Disorders [Sandberg 1987; Dickey 1976]

Cystitis (bladder infection) [See above]

Enuresis (Bed-wetting) [Gerrard 1976]

Glomerulopathy [Finn 1980; McCrory 1986] Finn reports increased occupational exposure to hydrocarbons among patients whose renal failure resulted from glomerular nephritis.

Nephrotic Syndrome [See above; also Sandberg 1977] Sandberg discusses six cases of severe idiopathic nephrotic syndrome which were related to milk ingestion.

13. **Rheumatologic Disorders** [Wojtulewski 1987]

Lupus Erythematosus [Reidenberg 1983] Reidenberg and coworkers report the case of a laboratory worker exposed to hydrazine who developed a lupus-like syndrome with arthralgias, fatigue, malar (cheek) rash, photosensitivity, antinuclear antibody, and antibodies to native DNA. Symptoms cleared away from work and returned when an in-hospital challenge test with hydrazine was performed. Her lymphocytes, but not those of three normal controls showed inhibition of mitogen-stimulated IgG synthesis following five daily exposures to hydrazine. Two major drugs, procainamide and hydralazine, which contain hydrazine moieties in their chemical structures, are widely recognized as causing lupus-like diseases. Hydrazine also occurs in a wide variety of natural and synthetic substances (over 30 million pounds of hydrazine are used by industry in the United States each year) such as mushrooms, tobacco smoke, plastics, rubber products, herbicides, pesticides, photographic supplies, textiles, dyes, and drugs [Reidenberg 1983]. Tartrazine (FD&C yellow No. 5) which is found in thousands of foods and drugs, can be metabolized to hydrazine compounds and has been associated in one case of a lupus-like syndrome.

Myalgia and Arthralgia [Randolph 1976e] According to Randolph, both osteoarthritis patients and rheumatoid arthritis patients improve when incriminated food and chemical incitants are avoided.

Rheumatoid Arthritis [Randolph 1976d; Panush 1986a, 1986b; Kroker 1984; Marshall 1984; Coombs 1981] In 1976 the American Arthritis Foundation concluded, "No food has anything to do with causing arthritis, and no food is effective in treating or curing it" [Skoldstam 1989]. However, some rheumatologists have identified a few patients who seem to benefit from special diets.

Kroker and Marshall describe a multi-center study conducted by clinical ecologists in which 43 patients with rheumatoid arthritis entered an environmental unit and underwent fasting followed by food challenge. Seven parameters of arthritic activity were measured and all significantly improved during the fast ($p = 0.001$). Following challenge with provoking foods in 27 patients, joint pain and circumference increased, while grip strength decreased ($p = 0.001$).

Panush, a rheumatologist, showed that rheumatoid arthritis improved significantly in 2 of 11 patients on a restricted diet (foods were not individually tested nor were patients in an environmental unit). In the two patients who improved, symptoms recurred when they deviated from their diet and double-blind food challenges demonstrated that specific foods exacerbated their symptoms. One wonders if more patients might have improved had foods been tested on an individual basis in a chemically-controlled environment, as was done in the clinical ecology study. The clinical ecologists followed a more strict elimination diet (fasting) than did Panush. In addition, chemical exposures were controlled since their patients were in an environmental unit.

In an interesting animal study, Coombs and Oldham placed rabbits on cow's milk instead of water for 12 weeks and induced knee joint synovitis, in some cases quite severe [Coombs 1981].

Other Arthritides [Randolph 1980, 130] Randolph is of the opinion that Reiter's syndrome, ankylosing spondylitis, psoriatic arthritis and other types of arthritis may also have environmental components.

14. Skin Diseases

Atopic Dermatitis (Eczema) [Pike 1987; Sampson 1986; Burks 1988] That IgE-mediated food sensitivities have a role in some cases of atopic dermatitis is gaining wider acceptance by allergists and dermatologists. Studies have shown that at least one-third of patients presenting to allergists or dermatologists with this condition have underlying food allergies [Burks 1988]. In addition to provoking skin symptoms, 30% of positive food challenges also resulted in gastrointestinal symptoms (nausea, vomiting, abdominal pain or diarrhea) and 52% in respiratory symptoms (wheezing, nasal congestion or sneezing). In select (referred) patients with eczema, Sampson found that foods provoked symptoms in about 56% of those who underwent double-blind, placebo-controlled food challenges [Sampson 1985].

Dermatitis Herpetiformis [Leonard 1987] It is widely accepted that dermatitis herpetiformis is associated with gluten sensitive enteropathy (celiac disease), and that gluten (e.g., from wheat) plays a causal role in both this rash and the enteropathy.

Urticaria [Winkelmann 1987] A wide variety of foods and additives, including caffeine [Pola 1988], are recognized by allergists as potential triggers for urticaria and exercise-induced anaplaylaxis. Contact urticaria and airway obstruction in response to carbonless copy paper have been reported [Marks 1984]. Delayed pressure urticaria has also been observed to clear during fasting and recur with food challenge [Davis 1986].

* * *

If, indeed, foods and chemicals are responsible for even a modest percentage of the diseases described above, the implications are staggering. As the preceding discussion indicates, there is a growing trend toward recognition of chemical and food factors in many diseases. Caution must be exercised, however. It may be that only a subset of patients with a particular illness, e.g. rheumatoid arthritis, respond to environmental manipulation. Even one individual who responds positively while fasting in an environmental unit can be an important finding if that finding is reproducible. Thus responses may occur only in a subgroup of sensitive patients and unless objective testing is limited to that sensitive subgroup, positive results in a few may be diluted by non-responders and prevalence studies will not be statistically significant. Clearly, studies of these patients must be carefully constructed if health effects are to be discerned.

One might ask how the disorders that have just been discussed relate to the concept of adaptation. This is unclear at present. Bell proposes:

> "...the chronic symptoms which ecology patients reportedly have with repeated exposures to offending agents may reflect the more insidious, non-adapting changes induced by offending foods and chemicals." [Bell 1982a, emphasis added]

For example, individuals may adapt to the acute effects of ozone on their upper and lower respiratory tracts, but red blood cell fragility may persist (see Section IVA). Others may adapt to the stimulatory effects of caffeine, only to develop fibrocystic disease [Russell 1989; Hindi-Alexander 1985; Boyle 1984] or urticaria [Pola 1988].

Randolph depicts the development of chronic illnesses in Table VII. On the left side of the table are intermittent (acute) responses, and on the right, chronic responses. At the top are stimulatory levels as discussed in Section IVA. With continued or repetitive exposures to an incitant, the course of the reactions moves from left to right. Over time, if no intervention occurs, advanced sustained stimulatory responses (upper right) ultimately move toward sustained withdrawal responses (lower right) [Randolph 1987, 248-249]. Rea speculates that adaptation may indirectly contribute to total body load by covering up [masking] acute reactions with chronic exposure responses so that the affected individual is unaware of the relationships between his exposures and his illness [Rea 1988c].

Thus adaptation could play a central role in the development of many medical disorders. Perhaps the best evidence thus far for the existence of adaptation in humans comes from de-adaptation, i.e., withdrawal of the individual from his environment and observing the loss of adaptation and simultaneous resolution of

ENVIRONMENTAL — PERSONAL INTERRELATIONSHIPS

	INTERMITTENT RESPONSES	LEVELS	SUSTAINED RESPONSES
SPECIFICALLY ADAPTED STIMULATORY LEVELS	MANIA (agitation, excitement, blackouts, with or without convulsions)	----	DRUG ADDICTION (both natural and synthetic)
	HYPOMANIA (hyperresponsiveness, anxiety, panic reactions, mental lapses)	---	ALCOHOLISM (addictive drinking)
	HYPERACTIVITY (restless legs, insomnia, aggressive forceful behavior)	--	OBESITY (addictive eating)
	STIMULATION (active, self centered with suppressed symptoms)	-	ABSENT COMPLAINTS (the desired way to feel)
	BEHAVIOR ON AN EVEN KEEL, AS IN HOMEOSTASIS	0	BEHAVIOR ON AN EVEN KEEL
SPECIFICALLY MALADAPTED WITHDRAWAL LEVELS	LOCALIZED PHYSICAL ECOLOGIC MANIFESTATIONS (rhinitis, bronchitis, asthma, dermatitis, gastrointestinal, genitourinary syndromes)	·	IMPAIRED SENSES OF TASTE AND SMELL MENIERE'S SYNDROME
	SYSTEMIC PHYSICAL ECOLOGIC MANIFESTATIONS (fatigue, headache, myalgia, arthralgia, arthritis, edema, tachycardia, arrythmia)	..	SMALL VESSEL VASCULITIS, HYPERTENSION, COLLAGEN DISEASES
	BRAIN FAG — MODERATELY ADVANCED CEREBRAL SYNDROMES (mood changes, irritability, impaired thinking, reading ability & memory)	...	MENTAL CONFUSION AND OBFUSCATION, MOROSE INEBRIATION
	DEPRESSION — ADVANCED CEREBRAL & BEHAVIORAL SYNDROMES (confabulation, hallucinosis, obsessions, delusions & temporary amnesia)	....	DEMENTIA, STUPOR, COMA, CATATONIA, RESIDUAL AMNESIA

Table VII. Intermittent and sustained stimulatory and withdrawal levels of physical and mental reactions

Source: Randolph 1980.

formerly chronic symptoms. This process is viewed optimally in the setting of an environmental unit while patients fast as discussed earlier in Section IVA.

In the next section we discuss some of the mechanisms that have been proposed for multiple chemical sensitivities.

V. POSSIBLE MECHANISMS, DIAGNOSTIC APPROACHES, AND THERAPIES[1]

A. POSSIBLE MECHANISMS

1. Possible Physiological Mechanisms

It is apparent from the limited data available at this time that any mechanism or model that would purport to explain the syndrome of multiple chemical sensitivities would need to address the following features which seem to be associated with this illness:

1. Symptoms involving virtually any system in the body, or several systems simultaneously.

2. Differing symptoms and severity in different individuals, even those with the same exposure.

3. Induction (i.e., sensitization) by a wide range of environmental agents.

4. Subsequent triggering by lower levels of exposure than those involved in initial induction of the illness.

5. Concomitant food intolerances, estimated to occur in a sizeable percentage of those with chemical sensitivities.

6. "Spreading" of sensitivity to other, often chemically-dissimilar, substances. Each substance may trigger a different constellation of symptoms.

7. Adaptation (masking), i.e., acclimatization to environmental incitants, both chemical and food, with continued exposure; loss of this tolerance with removal from the incitant(s); and augmented response with re-exposure after an appropriate interval (e.g., 4 to 7 days).

8. An apparent threshold effect referred to by some (including certain traditional allergists whom we interviewed) as the patient's "total load". Total load is a theoretical construct that has been invoked by clinical ecologists to help explain why an individual develops this syndrome at a particular time. Illness is said to occur when the total load of biological, chemical, physical, and psychological stressors exceeds some

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[1]For a useful review, also see Bell [1987b].

threshold for the patient. This concept has emerged from clinical observations; no direct experiments have been done to test its validity in humans; however, animal models do exist. The concept aligns with Selye's work on the General Adaptation Syndrome [Selye 1946].

Randolph knew Selye and was intrigued by his ideas, but failed to see their clinical utility. Selye defined stress as the "non-specific response of the body to any demand." His "General Adaptation Syndrome" was comprised of three parts: An alarm reaction; resistance (corresponding to Randolph's adapted stage); and exhaustion. Randolph's ideas differ from Selye's in one vital respect: Randolph observed that adaptation in a given individual was specific to the incitant. Although Selye apparently recognized this might be true, he focused more upon the general aspects of adaptation. Randolph considers his substance-specific and individual-specific view of adaptation to be the clinical counterpart of Selye's General Adaptation Syndrome [Randolph 1962, 6-8; 1976a].

Rea probably has performed more clinical laboratory tests on chemically sensitive patients than any other clinical ecologist. When we asked him what mechanism he thought was responsible for these patients' illness, he responded, "Which one?" In his view, there may be many interacting factors. No single biochemical or immunological abnormality appears consistently in every patient. Some may have abnormal levels of immunoglobulins, complement, immune complexes, T-cells, B-cells, prostaglandins, kinins, serotonin, histamine, acetylcholine, vitamins, minerals, or detoxification enzymes (such as glutathione peroxidase) [Johnson 1989]. Rea sees a great diversity of patients since he receives referrals of more difficult cases from other physicians. More clearly defined, homogeneous patient groups, such as those from a specific workplace, contaminated community, or tight building, might very well exhibit less variation in their laboratory profiles. (See discussion in Section VII.)

Before examining some of the specific theories which have been proposed to explain multiple chemical sensitivity, three important points must be recognized:

1. The human body is an integrated system which traditionally has been separated into its component parts or systems to facilitate study. Interactions of these parts are necessarily more complex. For example, multiple chemical sensitivities conceivably could involve the entire neuro-immuno-endocrine axis. Teasing out the subtle biochemical interactions involved in adaptation to the plethora of substances in the environment may be extremely difficult.

2. Traditional allergists who have studied sensitivity to industrial chemicals have been as baffled as the ecologists in trying to discern a mechanism for hyper-reactivity. Butcher, Salvaggio et al [1982] remarked upon the continuing controversy over the mechanism for isocyanate hyper-reactivity. Although an immunologic theory has been proposed, specific antibody is demonstrable in only 15-20% of reactive individuals.

Antibodies also may persist beyond loss of reactivity casting doubt upon their role. More recently, Stankus, Salvaggio et al demonstrated airway hyper-reactivity to cigarette smoke among asthmatics who lacked specific IgE to tobacco smoke components [Stankus 1988]. They report that the mechanism[s] behind this hyper-reactivity remains unclear. These observations concerning the effects of cigarette smoke on some individuals parallel similar observations by clinical ecologists.

3. Although knowledge of the mechanism of a disease may be useful for developing better therapies, such knowledge is not a prerequisite for intervention. It may be possible to prevent the development of multiple chemical sensitivities in those not yet afflicted by controlling environmental exposures.

The most frequently cited theories to explain chemical sensitivity involve either the nervous system or the immune system or the interaction between them, since these two systems most clearly link the external environment and the internal milieu [Bell 1982b]. The rapid responsiveness of these systems also makes them attractive candidates since symptoms of food or chemical sensitivity have been reported to develop within seconds of exposure. As early as the 1940's and 50's, Coca, an allergist, recommended sympathectomies (surgical interruption of certain sympathetic nerve pathways) in some cases of multiple food sensitivities but benefits were often short-lived [Randolph 1987].

Dr. David Ozonoff, Professor of Medicine and Chief, Environmental Health Section, Boston University School of Public Health, suggests that since low levels of exposure do not trigger symptoms in everyone, perhaps a small initiating stimulus occurs which the body then amplifies or magnifies in the chemically sensitive patient [Ozonoff 1989]. In the case of multiple chemical sensitivities, either the nervous system or the immune system or both might amplify an external signal. Many chemicals, e.g., polybrominated biphenyls (PBB's) and trichloroethylene, affect both the nervous system and the immune system. Until 1980, the idea that there could be direct communication between the nervous and immune systems was widely debated. Subsequently, it has been increasingly realized that a neuro-immuno-endocrine axis does exist. Payan cites several discoveries which have helped to confirm that there is two-way communication between the nervous and immune systems [Payan 1986, 1989]:

1) Studies show that neuropeptides (e.g., substance P and somatostatin) and the nerve ganglia from which they arise project into immunologic tissues.

2) Receptors for these neuropeptides occur on immunologically active leukocytes.

3) Certain immunologically active substances such as the interleukins can activate or be activated by cells in the nervous system.

4) Electrolytic lesions in the hypothalamus of animals produce distinct alterations in antibody production as well as abnormalities in the number and role of natural killer cells and T-lymphocytes. This occurs because of the interruption of a network of noradrenergic and peptidergic fibers that project into lymphoid tissues including the thymus, spleen, Peyer's patches of the intestine, and bone marrow.

Thus the endocrine and immune systems, once perceived as separate compartments are increasingly being recognized as interconnected.

The hypothalamus has attracted considerable attention since it is the focal point in the brain where the immune, nervous and endocrine systems interact [Bell 1982b]. Corwin described the hypothalamus as a "true marvel of microminiaturization." Within a few grams of tissue in the brain lie the body's "analytical laboratory, computer controller and hormone factory" [Corwin 1978]. Stereotactic surgical lesions made in the ventromedial nucleus of the hypothalamus suppress addiction and induce hypersensitivity to morphine in addicted rats [Kerr 1971]. Bell notes that while it is premature to assume a direct cause and effect relationship, one might speculate that the hypothalamus also could mediate food and chemical addictions in patients with multiple chemical sensitivities. The olfactory system has known links to the hypothalamus and other parts of the limbic system. This has led Bell to speculate that "the olfactory system, hypothalamus and limbic system pathways would provide the neural circuitry by which adverse food and chemical reactions could trigger certain neural, psychological and psychiatric abnormalities" [Bell 1982b]. Many different chemicals have been reported by clinical ecologists to trigger food binges, violence, or hypersexual activity. A model involving the hypothalamus could help to explain such behavioral changes in response to chemical exposures.

The hypothalamus is also the locus at which sympathetic and parasympathetic nervous systems converge. Many symptoms experienced by patients with food and chemical sensitivities relate to the autonomic (sympathetic and parasympathetic) nervous systems, e.g., altered smooth muscle tone producing Raynaud's phenomenon, diarrhea, constipation, etc. Recently, Rea and his co-workers have acquired an iriscorder (to be distinguished from iridology) from the Japanese who have used this instrument to measure pupillary reactivity in persons with organophosphate pesticide toxicity. A brief pulse of intense light evokes pupillary constriction (a parasympathetic response) followed by a dilatation (a sympathetic response). With the aid of this device, Rea and coworkers are attempting to monitor objectively sympathetic and parasympathetic nerve function in persons with chemical sensitivities.

In 1950, Randolph, collaborating with a surgeon patient of his, Harry G. Clark, published an abstract on the "acid-anoxia-endocrine theory of allergy". Clark, who had food sensitivities, felt that in view of the speed of acute food reactions, changes in electrolytes must be involved [Randolph 1987]. Clark knew that allergy was often associated with edema and that one-celled marine organisms swell when acidified;

from this he reasoned that since the end products of digestion are acids, perhaps in food sensitive individuals these acid products of catabolism accumulate intracellularly more rapidly than they can be neutralized by the more alkaline extracellular fluid (including pancreatic bicarbonate). He thus surmized that treatment with alkali salts, i.e., bicarbonate salts of sodium and potassium, might be helpful. Indeed, Randolph and Clark found that if alkali salts were administered shortly after an acute food reaction, symptoms were dramatically relieved for many patients. Almost thirty years later, this form of treatment is still used for acute food reactions by clinical ecologists because of its efficacy in many patients. [See further discussion under therapies.]

Immunologic alterations are another possible explanation for multiple chemical sensitivities. Animal experiments demonstrate immunotoxicity from halogenated aromatics, heavy metals and organochlorine pesticides [Cone 1987]. There are also growing data from accidental human exposures to aldicarb, polybrominated biphenyls (PBB's), dioxin and other toxins that chemicals can impact the immune system. Volumes have been written on the subject of immunotoxicology [Sharma 1981]. A recent book attempts to catalog the extensive published literature on the immuno-modulatory action of chemicals and drugs [Descotes 1986]. Of special concern to allergists and some clinical ecologists have been Levin's assertions that environmental illness is a disorder of immune regulation. He points to decreased T-lymphocyte helper-suppressor ratios in four (4) different populations exposed to environmental toxins [Levin 1987]. Figures 11-14, reproduced from Levin [1987], depict helper/suppressor ratios for these four groups:

1. Seventy-eight affected workers from a computer chip manufacturing plant in Albuquerque, New Mexico.

2. Twenty-one individuals who became sick after being exposed to high levels of PCBs over 5-10 years in Catachee, South Carolina.

3. Twenty-five patients from Woburn, Massachusetts, whose illness was associated with exposure to trichloroethylene and perchloroethylene in their water.

4. Ten individuals in Wisconsin who became ill after drinking water for 5 to 10 years that was contaminated with a variety of industrial dyes, solvents and pesticides.

Note that in all four figures (11 through 14) there is a shift to the left (decrease) of the ratio of helper to suppressor T-lymphocytes.

The Woburn, Massachusetts data (Figure 13) is taken from 25 surviving family members of leukemia patients, all of whom drank water from wells contaminated with industrial solvents. Not only did these individuals have a statistically significant reduction in their T-cell helper to suppressor ratios (1.49 versus 1.94 in controls, $p<0.01$), but 48% (11/23) also tested positive for auto-antibodies. In addition, 88% (22) had frequent or chronic sinusitis or rhinitis and 52% (13) had gastrointestinal

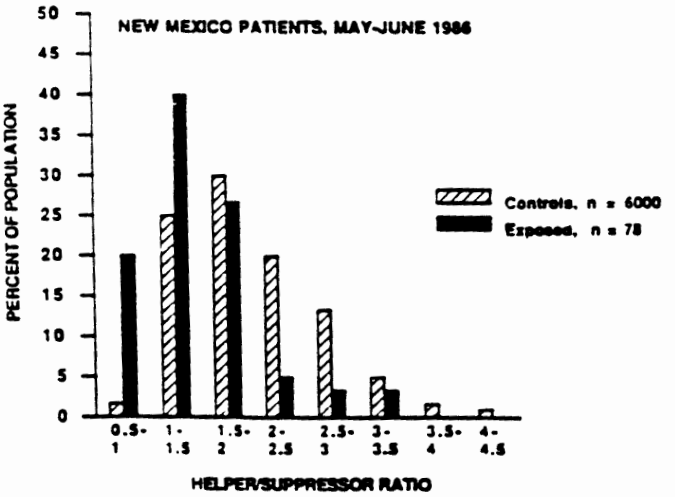

Figure 11. Helper/suppressor ratios obtained by standard clinical laboratory procedures on 78 injured workers from a computer chip manufacturing plant in Albuquerque, New Mexico compared with the standard laboratory control population of 6000 randomly selected asymptomatic people. The exposed population is statistically significantly different from the controls (chi-square = 39.34063; $p = 2.62 \times 10^{-6}$).[47]

Source: Levin 1987.

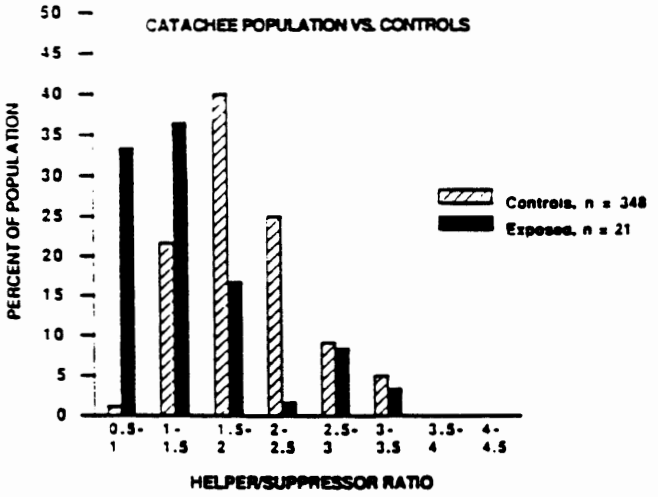

Figure 12 Helper:suppressor ratios obtained by standard clinical laboratory procedures on 21 environmentally ill patients who were domestically exposed to high levels of polychlorinated biphenols (PCBs) over a period of 5 to 10 years in Catachee, South Carolina, compared with the standard laboratory control population of 348 asymptomatic individuals. The exposed population is statistically significantly different from the controls (chi-square = 63.48208; $p = 1.37 \times 10<-6>$).[28]

Source: Levin 1987.

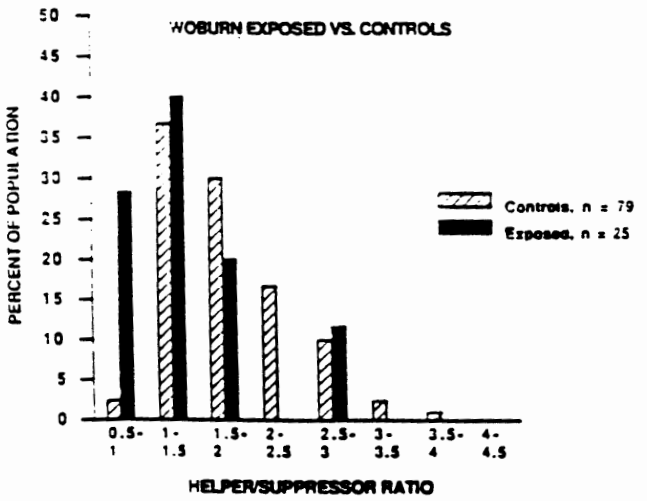

Figure 13 Helper:suppressor ratios obtained by standard clinical laboratory procedures on 25 environmentally ill patients from Woburn, Massachusetts who were domestically exposed to trichloroethylene (TCE) over a period of 5 to 10 years compared with age and sex matched asymptomatic controls.[7] The exposed population was statistically significantly different from the controls (chi-square = 42.18912; $p = <1 \times 10^{<-8>}$). This control population is not significantly different from the standard laboratory controls used in the other studies.

Source: Levin 1987.

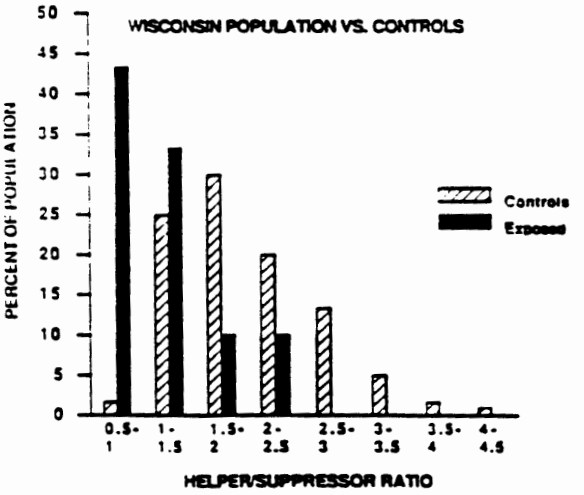

Figure 14 Helper:suppressor ratios obtained by standard clinical laboratory procedures on 10 environmentally ill patients from rural Wisconsin who were domestically exposed to a variety of industrial dyes, solvents, and pesticides over a 5 to 10 year period compared to the standard laboratory control of 6000 randomly selected asymptomatic people. The exposed are significantly different from the controls (chi-square = 73.58482; p = 4.77 × 10<−6>).[30]

Source: Levin 1987.

Reprinted with permission from Levin, A. and V. Byers, "Environmental Illness: A Disorder of Immune Regulation," in Workers With Multiple Chemical Sensitivities, M. Cullen, Ed. (copyright 1987, Hanley & Belfus, Inc., Philadelphia, PA).

complaints often described as irritable bowel syndrome. Rashes were frequent. Fourteen adults complained of rapid heart rate at rest, palpitation or near syncope, and eleven of these underwent cardiac workup. Of the eleven, eight had multifocal premature ventricular contractions and six were felt to need cardiac medications [Byers 1988].

What is remarkable are the many similarities between the Woburn data and data gathered by Rea et al on patients who have been worked up in the ecologists' environmental unit in Dallas [Johnson 1989]. Nineteen percent of 150 ecology patients were positive for anti-nuclear antibodies. Many others had antithyroglobulin or other auto-antibodies. In addition, the polysymptomatic complaints of the Woburn study group resemble those of the ecology patients. However, there are differences too. In 70 ecology patients with vascular dysfunction, the T_4/T_8 (helper/suppressor) ratio was increased (2.20) versus 60 controls (1.70) ($p=0.001$). Seven rheumatoid arthritis patients showed similar increases in T_4/T_8 while 27 asthmatics showed no significant differences from controls. It is unclear why certain individuals have increased T_4/T_8 ratios while others have decreased ratios. Perhaps there are some differences in the kinds of patients in these studies, the exact nature of their exposures, or the time elapsed since exposure. Interestingly, cigarette smoking, which is well recognized for its long-term adverse health consequences, recently has been linked to an increased number of T_4 (helper) cells ($p=0.002$) and an increased T_4/T_8 ratio ($p=0.02$) [Tollerud 1989].

Such data warrant further study. Levin has stirred considerable controversy among allergists and clinical ecologists. His focus on the immune system has drawn allergists/immunologists into the fray since this is their area of specialization. Levin and traditional allergists often serve as expert witnesses on opposing sides in lawsuits and disability evaluations. Terr asserts that immune parameters of patients who have seen clinical ecologists fall within expected normal ranges "except for several patients who had immunoglobulin (IgA) and lymphocyte levels above the normal range, reflecting a history of infections" [Terr 1986]. Levin counters, arguing that one would expect only 2.5% of the population to fall outside the normal range, while in Terr's data 20-30% of these patients fall outside the normal range [Levin 1989].

As can be seen from Figures 11 through 14, individual data points (a single individual's helper-suppressor ratio) may be difficult to interpret as normal or abnormal since the ranges for normal data are quite wide. However, when one looks at an entire exposed population, the data appear to be skewed to the left, that is, toward a reduced helper-suppressor ratio. Levin commented on some recent data suggesting that the reduced helper/suppressor T-lymphocyte ratios seen in many chemically exposed individuals may be the result of increased numbers of cytotoxic lymphocytes in the suppressor cell population of these patients [Levin 1989]. Such cytotoxic lymphocytes could be "reactively cloned in response to a somatically transformed cell," i.e., a cell somehow transformed by a chemical agent.

The idea that relatively low molecular weight chemicals can somehow alter native protein perhaps acting as haptens, and elicit a sort of auto-immune response to

that altered protein is gaining support. Formaldehyde [Thrasher 1987]; trimellitic anhydride [Akiyama 1984]; isocyanate [Butcher 1982]; hydantoins [Kammuller 1988] which are present in many drugs and foods; and hydrazine [Reidenberg 1983] which occurs in mushrooms, plastics, pesticides, tobacco smoke, various drugs, etc., all have been reputed to cause immune derangement, possibly by such a mechanism.

It is important that future governmental and scientific investigations include measurement of T- and B-cell numbers and other relevant immune parameters as possible indices of toxicity. Levin and others have helped draw attention to the need for these data.

Other indicators of immune system function have been examined for their relevance by clinical ecologists. Commonly, IgE levels are normal or even low in their patients, but some are elevated; abnormal activation of the complement system may occur; increased auto-antibodies may be present; lymphokines, prostaglandins, kinins and a host of other mediators may be affected, but again, none of these applies for all patients [Johnson 1989]. Rea and other ecologists have noted vitamin and mineral abnormalities in many of their patients [Johnson 1989]. Their detractors argue that these patients are often sick, debilitated, and malnourished; and therefore such findings are not surprising. Such a contention is difficult to disprove, even if incorrect.

An intriguing paper concerning the effects of aldicarb (a widely-used carbamate insecticide and nematocide) on the immune system of mice demonstrated that aldicarb in the drinking water suppressed the immune response (to sheep red blood cells) more at 1 part per billion than at 1000 parts per billion [Olson 1987]! This is a surprising departure from classic toxicologic dose/response curves where dose and toxicity increase together (see Section II). The experiment was carried out several times with two mouse strains and two sources of aldicarb, with the same result. The animals did not die or develop the opportunistic infections usually associated with immune deficiency; however, the authors comment that "such animals will usually not survive a frank challenge with a virulent microorganism." They speculate on the reason for the inverse dose/response curve for aldicarb:

> "This phenomenon may be associated with dose related detoxification/elimination in the intestinal tract or body, differential rates of clearance by the kidneys, or possibly the clearance of antigen aided by antibody (induced through conjugation of the chemical to naturally occurring proteins and followed by elicitation of specific antibodies." [Olson 1987]

Conceivably, then, lower levels of toxic substances could be more damaging than higher levels perhaps because damage from the former is so slight that usual cell repair mechanisms are not triggered and the damage becomes permanent. Individuals who have defective enzyme detoxification systems would be even more susceptible to lower level exposures. Rea has noted that many of his chemically sensitive patients have abnormal levels of detoxifying enzymes, such as glutathione peroxidase. This is a particularly intriguing possibility since such enzyme systems are inducible, i.e., can

be stimulated, and thus might conform to an adaptation hypothesis. Scadding et al noted poor sulphoxidation ability in 58 of 74 patients with well-defined reactions to foods versus 67 of 200 "normal" controls ($p<0.0005$) [Scadding 1988]. Similarly Reidenberg reported the case of a laboratory technician who developed a lupus-like disease in response to hydrazine [Reidenberg 1983]. She was genetically a slow acetylator and this, it was felt, might have predisposed her to developing a lupus-like disorder after sufficient exposure to an inciting chemical. A deficiency of a particular enzyme[s] could help to explain why some patients are more susceptible to foods and chemicals than others. Further, damage by a toxin might compromise detoxification pathways so that other substances formerly metabolized by this pathway could not be degraded properly, and thus might provoke symptoms at low exposure levels (a hypothetical basis for the spreading phenomenon).

A final comment regarding the association of food sensitivities with chemical sensitivities: It must be remembered that foods are aggregates of chemicals [Bell 1982b; Kammuller 1988]. The human diet is an important source of exposure to both low and high molecular weight compounds. Antibodies to foods are present in the blood of many individuals, attesting to the fact that molecules from foods do leave the gut and enter the bloodstream. Thus, any mechanism for the development of sensitivities which might be proposed for chemicals could pertain to foods as well. Butcher, Salvaggio et al evaluated a worker with TDI sensitivity who could not eat radishes [Butcher 1982]. One bite of a small radish caused severe, immediate bronchoconstriction with a 75% decrease in FEV_1 five minutes after challenge, necessitating epinephrine treatment. Twenty-six months later when this individual was again able to tolerate isocyanates, he was challenged with 14 grams of radish with no ill effects. The authors note that radishes contain allyl isothiocyanate and benzyl isothiocyanate. However, these chemicals are also present in other foods which the patient was able to eat without adverse effect. This example is illustrative of a possible connection between sensitivities to environmental chemicals and sensitivity to particular foods. Many similar cases of coexisting food and chemical intolerance have been cited by clinical ecologists; however their work is often dismissed as "anecdotal." It is only through observations like these that one can discover patterns, which in turn suggest an hypothesis, which then leads to experiments to prove or disprove that hypothesis. We are currently at the pattern-recognition stage with regard to multiple chemical sensitivities. Finding a mechanism[s] to explain these patterns lies down the road.

2. Possible Psychiatric Mechanisms

Only a decade ago, when news of the first cases of Tight Building Syndrome reached the public, some psychiatrists and psychologists were quick to attribute the subjective complaints of individuals exposed in these buildings to "mass hysteria" or "mass psychogenic illness". In 1979 NIOSH held a symposium entitled "The Diagnosis and Amelioration of Mass Psychogenic Illness." One of the authors of this report presented a paper entitled, "Mass Psychogenic Illness or Chemically Induced

Hypersusceptibility?" at that symposium [Miller 1979]. The presentation was devoted to a discussion of subjective symptoms provoked by exposure to low levels of chemicals. The paper sparked a great deal of controversy. The same conference today would more likely be entitled "Indoor Air Pollution" since there is now widespread recognition of this phenomenon. For the most part, mass psychogenic illness faded from view.

Several of the traditional allergists whom we interviewed remarked that it is becoming increasingly difficult for them to find psychiatrists willing to see patients with these sensitivities, since psychiatrists and psychologists are being "wooed" by the clinical ecologists. Other psychiatrists strongly feel individuals with multiple chemical sensitivities suffer from atypical depression, hypochondriasis, post-traumatic stress disorder, hysteria, panic disorder, conversion disorder, or combinations of these [Schottenfeld 1987; Brodsky 1987]. Examples of psychiatric interpretations of multiple chemical sensitivity are as follows:

> "...the early childhood history of individuals with M.C.S. [Multiple Chemical Sensitivities] is often notable for the presence of physical or sexual abuse, severe medical illness during childhood, death of one or both parents, or other severe disturbances of early care-giving relationships." [Schottenfeld 1987]

Further advice is offered by this psychiatrist to physicians who work with these patients:

> "Regardless of the original etiology of symptoms, these individuals tend to amplify their symptoms and to develop the mistaken belief that the symptoms are indicative of severe disease." [Schottenfeld 1987]

> "Changes in the workplace that reduce toxic exposure and the risk of exposure may provide the most reassurance - the installation of a new exhaust system in Mrs. A.'s workplace was an extremely effective psychotherapeutic intervention in addition to its obvious benefit in the prevention of occupational respiratory disease." [Schottenfeld 1987, emphasis added]

> Another psychiatrist writes:

> "A review of medical history and literature that reflects on medical cultures reveals that there have always been people who have had unpleasant physical and emotional symptoms and experiences for which they sought explanations....In the culture of 20th century medicine, a disorder of the immune system would represent a sophisticated and acceptable explanation, because the immune system is demonstrably complex and is inter-related with all other systems, and no one would disagree that many of its mechanisms and manifestations are still unknown." [Brodsky 1987]

Psychiatric diagnoses are virtually untestable; in our view it would be preferable to rule out chemicals as a possible cause for patients' problems before resorting to psychiatric diagnoses. An environmental unit is the key to a definitive diagnosis.

The symptoms of low-level chemical exposure may include depression, difficulty concentrating, anxiety, peculiar bodily sensations, headaches, and other subjective symptoms. Patients with multiple chemical sensitivities often report that before they understood what was causing their symptoms, they felt as if they could not trust their own bodies or feelings. At any moment, they might feel fine, making plans and commitments for the future; then, the next day, or even later the same day, feel lethargic, unmotivated, headachy, sleepy, and depressed, as if they had flu. Suddenly, they are unable to fulfill commitments made when they felt energetic. These ups and downs are frequently interpreted by psychiatrists as responses to psychosocial stresses, and patients may be willing to accept such insights, lacking a better explanation. Patients who have been worked up in an environmental unit, on the other hand, often say they are amazed to find direct, clear-cut, cause-and-effect relationships between their symptoms and various foods and chemicals. For the first time, they say they are able to discriminate between their real feelings and those triggered by chemicals. Afterwords they report that their emotions are appropriate to the situation thereafter, unless, of course, they are having a reaction to a chemical. Not infrequently such patients feel hostility toward the physicians and psychiatrists who for so long overlooked the chemical basis for their symptoms and instead attributed them to psychiatric causes. These patients wonder how it can be that psychiatrists, who routinely use minute doses of chemicals called "drugs" to effectuate behavior, fail to recognize that chemicals in the air or foods can impact the brain or cause marked behavioral changes.

It is unquestioned that enzymes and various nutrients, e.g., vitamins and minerals, act as biological catalysts and regulators. Clearly, any disruption of their function by environmental chemicals might have diverse and far-reaching effects. The limitations of medicine's ability to understand the health complaints of these patients must be honestly and fully acknowledged so that these patients' symptoms are not dismissed as psychiatric when in fact physicians are just beginning to understand the gamut of effects of chemicals on the brain and central nervous system.

Some authors have alleged that psychological conditioning to odors is responsible for patients' reactions to chemicals. There is no argument that odor conditioning may occur in selected cases. However, patients experience reproducible symptoms to specific chemical exposures (1) often before the odor is perceived, (2) with nose-clamping during provocative testing, and (3) when anosmia is present [Shim 1986]. These observations weigh heavily against classical conditioning as any more than a partial explanation in certain patients. A direct pathway from the oropharynx to the brain and hypothalamic and limbic region has been demonstrated in rats [Kare 1968; Maller 1967]. Substances placed in the oropharynx migrated to the brain in minutes via a pathway other than the blood stream, and in higher concentrations than

if administered via the gastrointestinal tract, suggesting a direct route from mouth (or nose) to brain.

Results of psychological tests also may be misleading in these patients. For example, the Minnesota Multiphasic Personality Inventory (MMPI), a widely-used psychological instrument, includes questions concerning peculiar bodily sensations, feelings of inappropriateness, depressed feelings, and many other symptoms, all of which may result from chemical exposures. The chemically sensitive patient who has such symptoms may "read out" as depressed, hypochondriacal, or hysterical on MMPI scales when, in fact, depression, hypochondriasis and hysteria might not be the cause but rather the result of their food and chemical sensitivities.

A study of 42 patients admitted to the Dallas environmental unit employed a battery of clinical instruments including the MMPI and the Weschler Adult Intelligence Scale - Revised (WAIS-R). Analysis of test results, before and after entering the unit and being on "safe" foods, showed "statistically significant and clinically meaningful" improvement in 5 factors: "alienated depression, ineffectiveness, effortful processing, vigilance and effective energy". According to the authors, depression lifted, mental acuity improved, feelings of despondency and hopelessness resolved, concentration and short term memory increased, and energy returned [Bertschler 1985].

Clinical ecologists do not argue that certain patients may not have true psychiatric illness. As medical practitioners sometimes say "dogs can have both ticks and fleas," an unflattering reference to the possible simultaneous presence of two diseases in certain patients. The difference between the psychiatric model and that of the clinical ecologist is that clinical ecologists insist upon ruling out food and chemical sensitivities prior to applying a psychiatric label to their patients. To clinical ecologists, the vast majority of psychiatric and neurological symptoms their patients experience are the result, not the cause, of their chemical hypersensitivity.

* * *

It is possible that the mechanism for multiple chemical sensitivities is not identifiable, i.e., after all avenues of biochemical and immunological inquiry have been exhausted, no single explanation for this disorder is forthcoming. The theory of substance-specific adaptation is based upon observations of the responses of patients worked up in an environmental unit, in a de-adapted state. Adaptation is only an observation at this time, not a mechanism. However, it would not be unreasonable to consider that there might be biological limits with respect to how much an organism can adapt, limits that could be highly individual and vary by orders of magnitude. Certainly adaptation occurs at all levels of biological systems, from enzyme systems to cells, tissues, organs and even behavior [Fregly 1969]. Theoretically, a major insult or the accumulation of lower-level injuries within these systems could lead to a kind of "overload" or "saturation" effect with respect to adaptive capacity, leaving an individual whose environmental responses, instead of being flexible and fluid, are now fragile and overly responsive. Many patients we interviewed for this report told us

that even years and in some cases decades following the onset of their problems they recovered only a portion of their former energies and tolerance for their environment. Their descriptions seem to suggest the loss of an intangible capacity to adapt, parts of which may be temporary and recoverable, others of which may not. We are reminded here of the teaching "Listen to the patient. He is telling you the diagnosis." Perhaps they are telling us the mechanism as well.

B. DIAGNOSTIC APPROACHES

As with most fields in medicine, meticulous history-taking is the most important element in making a diagnosis. However, history-taking for multiple chemical sensitivities involves not only obtaining a chronology of illness but exposures as well. "Although the physical examination is an integral part of all medical investigation, 'examination of the environment' of a patient tends to be relatively more rewarding...." [Randolph 1987, 274]. Physicians today must ask their patients what kind of work they do, as well as inquire about specific chemical exposures on or off the job or changes in symptoms at work, on weekends or during vacations. Ramazzini, the father of occupational medicine, instructed physicians to ask "Of what trade are you?" On the whole, occupational health practitioners today, more than other medical specialists, take the most comprehensive exposure histories. Thus for patients who may have multiple chemical sensitivities resulting from industrial, tight-building or community exposures, the physician-group most attuned to and therefore likely to discover the potential link between the patient's illness and a chemical exposure is the occupational physician. The "new generation" of occupational health physicians is well-informed about chemicals, various processes and associated exposures, as well as signs and symptoms resulting from chemical exposure [Rosenstock 1981]. They are familiar with the industrial hygienists' measurement of chemical exposure. However, before they can help chemically sensitive patients they will require instruction in the particular symptoms, provoking exposures, and special problems of these patients. Occupational health physicians and clinical ecologists have overlapping interests and would benefit from exchanging information and cross-training. Likewise, allergists, by learning more about chemicals and toxicology as recommended by some of their spokesmen [Selner 1985b; Bardana 1989] and by taking exposure histories that go beyond the confines of IgE-mediated disease, could emerge as a major physician-group specializing in the problems of these patients in the future.

An adequate exposure history with attention given to pinpointing when symptoms began in relation to other factors, e.g., drugs, chemical exposures, job changes, household moves, hobbies, etc. is essential. This time-consuming detective work is the sine qua non for discovering an inciting exposure. Properly designed patient questionnaires may facilitate the process, enabling the patient to engage in the detective work as well. Questions concerning the patients' likes or dislikes for certain odors may be revealing since aversion to particular odors has been noted commonly among patients who have multiple chemical sensitivities [Randolph 1980]. Over the years, Randolph has noted that the more odors checked off on the questionnaire as "strongly like" or "strongly dislike," the more likely the patient has chemical sensitivities.

Of course, the more symptoms and the more systems of the body affected, especially the nervous system, the stronger should be the physician's suspicion of multiple chemical sensitivities. Rea et al report that the average patient entering the Dallas environmental unit has five symptom complaints, many of which are neurological [Johnson 1989]. Industrial workers with multiple chemical sensitivities

exhibit similar constellations of symptoms [Cone 1987]. A history of multiple "idiosyncratic" drug reactions may also be suggestive. [See Section IV B 5.]

The physical exam, traditionally an important diagnostic tool, disappointingly is often normal in these patients. Symptoms may occur only with exposure. Signs may be subclinical and pre-pathologic. Laboratory findings may be normal or, if abnormal, provide no pattern or clue that seems to have clinical relevance. Altered helper/suppressor T-lymphocyte ratios and the presence of auto-immune antibodies may be suggestive (see Section VA). Subtle signs of vasculitis are noted in some; spontaneous bruising, petechiae and cold or blue extremities (Raynaud's phenomenon) may occur.

Rea has noted yellowish skin discoloration with normal liver function tests in some patients and refers to this as the "chemical yellows." Allergic shiners, Dennie's lines [creases under the eyes], reddening of the ears, and the 'allergic salute' (nose rubbing) might provide clues in some children [Rapp 1986]; these facial features are recognized by allergists in children with both classical IgE-mediated allergy and non-allergic, non-IgE rhinitis (etiology of the latter is unknown but conceivably could be related to food or chemical exposures).

Rea et al are exploring more sophisticated and objective ways of measuring changes in their patients, e.g., monitoring sympathetic and parasympathetic nervous system activity by recording pupillary reactions to a light stimulus (discussed in Section VA); and using a balance recorder, a platform on which the patient stands and attempts to maintain balance. Movements of the patient are recorded and reflect disturbances in one or more of the three physiological inputs that regulate balance: visual input, the inner ear and proprioceptive signals.

As discussed in detail in Section IVA, the gold standard for diagnosing chemical hyper-reactivity in a patient is the environmental unit, coupled with fasting. This concept is fundamental to our ultimate understanding of multiple chemical sensitivities. Although this approach may be too costly and time-consuming for the average patient, for the very ill, it may be the only way to unravel this multifactorial, polysymptomatic illness.

Short of a several-week stay in an environmental unit, is there any other approach that can be used to diagnose chemical and food sensitivities, for example, in patients who do not require hospitalization or who may wish to be worked up as outpatients? Certainly an elimination diet can be attempted to identify food incitants. Patients may have difficulty fasting or avoiding common incitants, rotating their foods or obtaining chemically less contaminated foods. (Even so called organic foods may not be entirely free of pesticides and other contaminants.) Detecting subtle chemical sensitivities while at home is even more difficult. "Masking" or adaptation to chemicals in one's home environment (e.g., gas furnace emissions) may go unrecognized. If comprehensive environmental control is attempted at home, major remodeling or overhauling of furniture, heating systems, wardrobe, etc. may be required in order to achieve a chemically less contaminated environment for the

patient. Such interventions if done in a "hit or miss" fashion could be costly. It would be far better to have residences that are relatively "safe" habitats, e.g., specially constructed trailers or homes, in which patients could reside temporarily while they "sort out" their sensitivities and undergo food and chemical testing. The authors of this report visited a small community of patients outside of Dallas where such homes are occupied by chemically sensitive patients, and inspected trailers lined with porcelain that have been specially constructed for chemically-sensitive individuals.

Clearly, the cost and trouble of such a rigorous diagnostic approach may be prohibitive for the average patient with chemical sensitivities. For this reason, provocation-neutralization has been promoted by ecologists as a way to diagnose and treat at least some of their patients' sensitivities to biological inhalants, foods, and chemicals. This procedure will be considered in detail in the next section, which discusses therapies.

Less widely accepted and far more controversial diagnostic approaches used by the minority of clinical ecologists include electro-acupuncture, kinesthesiology and others. The basis for these procedures is speculative at best; they will not be addressed in this report.

C. THERAPIES

To the traditional practitioner, perhaps the most disturbing feature of clinical ecology is the wide range of therapeutic modalities used by various practitioners and the lack of proof for many of them. Many allergists with whom we spoke expressed frustration with an attitude among certain clinical ecologists that they do not need science because they are right. Allergists are critical of clinical ecology's lack of randomized, double-blind clinical trials. Randolph and other ecologists feel this criticism is "overdrawn" [Randolph 1987, 220]. They emphasize the clinical nature of the field: its concepts and techniques are inductively derived from careful clinical observation. As rigorous and cautious as Randolph's use of an environmental unit might have been, the same cannot be said for other treatment approaches used among clinical ecologists. We will discuss here some of the more frequently used therapies by ecologists including provocation-neutralization; nutritional supplementation; detoxification and the treatment of acute reactions to foods and chemicals. Fundamentally, clinical ecologists agree that avoidance of incitants, both food and chemical, is the treatment of choice and allows the best possibility for recovery. Clearly, however, this is not entirely satisfactory. Avoidance can lead to an ascetic lifestyle that is unacceptable to many patients. Some, who are very ill, feel they have no choice. A number of treatment modalities have been employed by ecologists in an attempt to speed their patients' recoveries; however, it must be emphasized that no study has been done to demonstrate whether patients receiving these treatments recuperated any faster than if they had practiced avoidance alone.

1. Provocation-Neutralization

The majority of clinical ecologists use provocation-neutralization to a greater or lesser extent. This technique involves provoking a patient's symptoms by injecting or administering sublingually a small dose of an inhalant, food, or chemical while observing the patient for symptoms and/or increase in wheal size if given via a cutaneous route. This "diagnostic" test is used to identify incitants for a particular patient. Subsequently, various dilutions of the same substance that produced symptoms or a wheal are injected or given sublingually until one dilution is found that will "turn off" the patient's symptoms, or that results in no increase in wheal size following intradermal injection. This dose is called the "neutralizing dose".

We will not attempt a lengthy review of all of the studies of provocation-neutralization done to date. That is beyond the scope of this report. Further, we feel strongly that too much emphasis has been placed upon trying to disprove this method as if the existence of the problem of multiple chemical sensitivities depended on provocation-neutralization. The existence of multiple chemical sensitivities and the efficacy of provocation-neutralization are independent issues and ought to be treated as such.

Suffice it to say that provocation-neutralization is an evolving technique, just as classical allergy testing is still evolving. Salvaggio, an allergist, has remarked upon the paucity of evidence to support the efficacy of mold immunotherapy that is used by classical allergists [Salvaggio 1981]. Others offer similar views:

> "Immunotherapy has been used empirically over the past 70 years, primarily because the actual immunologic mechanism has continued to elude investigators." [Gurka 1988]

> "The mechanisms by which hyposensitization is achieved are not completely understood....While statistically controlled blinded studies on the efficacy of allergens and immunotherapy have been made, for the most part, only for some pollens, extension of these results to other allergens and certain conditions is generally considered acceptable." (Package insert from an allergenic extract)

Immunotherapy was used by allergists for decades before the discovery by IgE by Ishizaka in 1969. Controlled trials demonstrating its effectiveness have been available only since the 1950's. Van Metre and Adkinson describe the difficulties faced by investigators who wish to design controlled trials for testing the efficacy of immunotherapy:

> "Design requirements are complex and difficult to accomplish in any one single trial. These difficulties can be addressed by developing a model of specific aeroallergen disease with which multiple groups of investigators can work over a relatively long period of time. Methods and reagents are refined until consistent, accurate results are achieved." [Van Metre 1988, 1329]

Such trials are difficult and costly to conduct. Large, homogeneous groups of patients must be recruited, for example, a large number of patients with seasonal hay fever triggered by ragweed pollen. Here each patient has the same symptom resulting from the same exposure. The added complexity of multiple symptoms resulting from many divergent exposures (as occurs in multiple chemical sensitivities) is obvious. The same authors recognize that trials using provocation-neutralization have had major problems with reproducibility, non-standardized extracts, non-homogeneous patient populations and disparate methods of measuring outcome; yet they comment favorably on studies by Boris using provocation-neutralization in two randomized placebo-controlled double-blind cross-over studies for cat and dog extract causing asthma [Boris 1985; see also Boris 1988], commenting that "the work deserves careful study and attempts at replication." Their comments contrast sharply with the position paper by the Academy on this subject:

> "Subcutaneous provocation and neutralization as a method for the treatment and diagnosis of allergic disease has no plausible rationale or immunologic basis." [American Academy of Allergy 1981]

A recent and comprehensive study of provocation-neutralization was supported by the American Academy of Otolaryngologic Allergists (AAOA) and reported in Otolaryngology - Head and Neck Surgery, a leading ENT journal. There are approximately 1800 members in AAOA who use these methods and these methods are endorsed by the 8000 members of the American Academy of Otolaryngologic Head and Neck Surgery, the largest group of ENT physicians in the country. Dr. William King's studies, sponsored by the AAOA, showed that provocation-neutralization had a sensitivity of 79.7% and a specificity of 72.4%, in contrast to classical skin testing which had a sensitivity of only 26.6% and specificity of 85.5% when compared with a provocative food challenge [W. King 1989, 1988a, 1988b]. In his 1986 Presidential address to the American Academy of Allergy and Immunology, Dr. John Salvaggio referred to "'fringe element' societies such as the otolaryngologists' allergy society, in which unproven methods of immunodiagnosis and therapy are used" [Salvaggio 1986]. Otolaryngologists who practice provocation-neutralization are not appreciative of the organized write-in campaigns by allergists which have successfully persuaded the Health Care Financing Administration to deny payment for provocation-neutralization for foods. Some merely regard these campaigns by the allergists as a "turf battle" between the allergists and clinical ecologists.

Sublingual provocation and neutralization is used much less often than injection techniques. Blinding is more difficult for sublingual provocation than for injection. Moreover, many ecologists feel that the clinical result is not as good. Nevertheless, sublingual testing and treatment have high patient acceptance and low risk of adverse reactions. Recent sublingual treatment studies using house dust mite [Scadding 1986] show promise for this approach. Although many think the venous network beneath the tongue is responsible for uptake of foreign substances, research using animals points toward a more direct pathway between the oropharynx to the brain (e.g., the hypothalamus) involving very rapid substance transport [Kare 1968; Maller 1967]. Such a mechanism might help to explain the rapid alterations in mental status patients report with provocation and neutralization by the oral route, as well as the rapid onset of symptoms they experience when ingesting or inhaling incitants.

The definitive study of provocation-neutralization has not yet been done. Nor have the studies purporting to prove its ineffectiveness been free from substantial flaws. Most convincing are individual cases in which symptoms appear dramatically with provocation [Miller 1987; Rapp 1978a, 1978b]. It may be that the technique works best in a select subgroup of patients. Indeed, the collective strength of the dozen or so positive studies may be greater than that of any individual study; the statistical technique of meta-analysis may have relevance here as a tool for evaluating them further [Louis 1985; Wachter 1988].

Dr. David King has carefully reviewed studies of provocation-neutralization and his work is important reading for anyone wishing to understand this subject [D. King 1984, 1988]. He reviews two of the studies that the American Academy of Allergy and Immunology relied upon for its position statement against provocative testing [1981]. One was a study by Caplin sponsored by the American College of Allergists [Caplin 1973]. King re-analyzes Caplin's data [D. King 1984] and finds that

the reported statistical analysis was incorrect. In fact, the validity coefficient is significant, implying that results of provocation were related to results of feeding challenges. Similarly, King examines a study by Lehman [Lehman 1980] which reported that sublingual testing was not reliable. Lehman did not analyze the data statistically to reach this conclusion. King found that the testing was in fact reliable for two of the four foods tested even though a very restrictive dependent measure was used for evaluation (nasal mucosal changes for which the reliability of the experimenter's judgement was unknown). King concludes: "A close examination of other frequently cited evaluation studies reveals similar flaws, making firm conclusions about provocative testing premature" [D. King 1984]. In another paper King reviews other studies which have found provocative testing unreliable or invalid, including the often cited study by Jewett which has been published in abstract form only [Jewett 1985]. In Jewett's study three "active" and nine placebo intradermal injections were administered to 18 clinical ecology patients reported by their ecology physicians to be sensitive to particular food extracts. Small doses ("underdoses") of food injections were administered double-blind and the subjects guessed which were active and which were placebo. The study concluded that results of guessing by subjects were no better than chance. King raises several important concerns about the Jewett study [D. King 1988]:

1. Patients may have been avoiding the food in question and thus have lost their prior sensitivity (see Section IVA regarding adaptation).

2. The use of an "either-or," dichotomous measure (guessing active or placebo) coupled with single-subject data analysis will detect only relatively strong effects and may work only for a highly accurate test, not one prone to a certain amount of error.

3. It is possible that underdoses are ineffective, while larger doses may provoke reactions in some patients.

4. The Fisher's exact test used to analyze the data is usually recommended for between-group studies, not repeated measures.

King himself conducted a study of provocation testing and found that allergenic extracts, under double-blind conditions could provoke cognitive-emotional symptoms in selected individuals [D. King 1981]. However, his enthusiasm for provocation-neutralization is carefully tempered. He notes that symptoms are frequently reported by subjects given placebos, "a finding which should concern clinicians employing the test" [D. King 1988]. King concludes:

> "Most studies of provocative food testing contain serious flaws which limit inferences regarding reliability and validity. Thus, whether these tests are sufficiently reliable and valid for clinical use cannot, strictly speaking, be determined from the research available, since the appropriately designed studies have not yet been conducted. However, the research that has been reviewed would seem to suggest that both

> methods of testing can provoke symptoms above placebo levels, but that these effects are generally quite small. Such subtle effects, when combined with symptoms that naturally vary over time and with placebo effects, would make it unlikely that their use in the clinical setting is as accurate as some proponents claim. On the other hand, the data do not support the conclusion that these methods cannot provoke genuine symptoms. Rather, the problem is distinguishing the "signal" from the noise. Averaging across many trials, as in group research, aids this process, but this fact is of little use in the clinic, in which every individual test is interpreted." [D. King 1988]

Provocation-neutralization may be in the beginning stages of its evolution, much like traditional allergy immunotherapy was earlier this century. Patients should not be held hostage by the controversies in this area. With so few available therapies, those that may offer benefits should not be barred, but investigated further providing no harm is done. Both otololaryngologists and ecologists realize there are limitations to provocation-neutralization's effectiveness. Rea, who probably sees the most severe patients, finds 30-40% of patients are not helped by provocation-neutralization techniques [Rea 1989], but feels that this should not preclude its use in the 60-70% who may receive benefit. Most clinical ecologists continue to stress the importance of avoidance as being the primary and most efficacious treatment with concomitant use of a rotary diet, but of course compliance may be difficult for many patients. Provocation-neutralization might prove useful with further study and development.

We asked several ecologists whether, by using neutralizing doses on a frequent basis, one might not simply be "masking" patients' symptoms, i.e., inducing adaptation that might obscure chronic damage caused by administering incitants on a regular schedule. There was concern over this point; however, most felt there was a big difference between a patient's taking neutralizing doses on a daily basis and eating the food on a daily basis. They argue that the former generally would not result in symptoms while actual food ingestion would.

Even if one were to accept provocation-neutralization as valid, extension of this technique from inhalants and foods to chemicals, such as formaldehyde, automobile exhaust, phenol, and tobacco smoke, is a major leap of faith and one that also needs much further investigation. Exposing patients to levels of chemicals normally encountered in everyday life may be justifiable. However, injection of potentially carcinogenic substances such as formaldehyde or auto exhaust is of considerable concern. Ecologists argue that their patients are exposed to these substances anyway and low doses will not increase risk to any measurable degree.

If provocation-neutralization were to be established as efficacious in clinical trials, evaluation of its long-term efficacy (the longest trials have been on the order of a few weeks) versus avoidance alone would be a next, important step.

One further consideration with regard to provocation-neutralization: the background level of pollutants in the testing room or those brought in on patients'

clothing or skin, (e.g. traffic exhaust, cigarette smoke) might interfere with accurate provocation and/or neutralization. In addition, the time interval since the patient was last exposed to the test substance may affect the provoking and neutralizing doses just as an individual's response to ozone or other substances may be affected greatly by recency of exposure (see Section IVA). Thus, adaptation or acclimatization must be considered as a potentially important, if not crucial, variable. If the testing room where provocation-neutralization is being done contains volatile organic compounds, cause and effect relationships may be obscured. At present, there is no reason to suppose that skin testing or sublingual testing is any different in this respect from oral or inhalation challenges conducted in an environmental unit. Background levels and the time interval since the last exposure to a substance must be rigorously addressed in any future studies.

To some, the most convincing bits of evidence in favor of provocation-neutralization come from the many "anecdotal" cases reported by ecologists. Dr. Doris Rapp has filmed several such cases using double-blind procedures. Nevertheless, traditional allergists raise concerns about appropriate control of conditions and her objectivity. Some discount her work, implying that the adults must be acting and the children either hungry or in need of a nap. We wonder whether these "anecdotal" cases, in which reactions to foods or chemicals can be turned on or turned off by a tiny amount of incitant, might not represent individuals whose sensitivity is very high and thus the reaction is easily observed. If so, these individuals present a unique opportunity to study and document this phenomenon. Provocations in these individuals must be done with sufficient iterations to satisfy statistical requirements as was attempted by Jewett in his study of provocation-neutralization [Jewett 1985]. Again, the effect of background noise on the testing must be assessed since inadvertent exposures (food or chemical) may interfere with test results. Perhaps such testing is most sensitive and specific if performed on patients in the de-adapted state in an environmental unit where background noise is negligible.

2. Detoxification

The EPA, in its ongoing program to monitor levels of toxic chemicals in human adipose tissue, has found many volatile organic compounds and pesticides in all parts of the body, including the brain and nervous system. Some of these chemicals may persist for decades; for example, beginning in 1973, Michigan residents were exposed to PBB (polybrominated biphenyl), a toxic fire-retardant, that accidentally had been substituted for a nutritional supplement in farm animals [Wolff 1982]. A clinical research team from Mount Sinai School of Medicine found that 97% of more than 1000 residents in the State had detectable PBB in their fat (0.2 ppb or more). Since serum levels taken 12 to 18 months apart in 1977-1978 were not significantly different, the researchers concluded that PBB in their tissues would remain there indefinitely. [Wolff 1979]

A detoxification method employing sauna, exercise, poly-unsaturated oils and various nutrients, that has been used in the field of drug rehabilitation for drug accumulations in fatty tissue was offered to 7 healthy male volunteers from Michigan. Following the detoxification regimen, fat biopsies from these individuals showed significant reductions in 16 chemicals (averaging 21.3% reduction), including PBBs. Four months later, after no further treatment, the same subjects nonetheless had additional decreases in chemical fat stores: The average decrease in the 16 chemicals studied was 42.4%. Schnare of the EPA and others hypothesized that this continued decline might suggest recovery of the body's own ability to eliminate toxic substances [Schnare 1984]. Others have reported use of detoxification therapy for dioxin toxicity [Roehm 1983]. Specifically, the detoxification regimen involves seven components [Schnare 1982]:

(1) Aerobic exercise for 20-30 minutes to increase fat mobilization;

(2) Low temperature sauna (140-180°F) for 2 or more hours (preferably 5 hours) after exercise to enhance skin excretion of toxic substances;

(3) Nutritional supplements with gradually increasing amounts of niacin to enhance lipolysis; and proportionate amounts of other vitamins and minerals.

(4) Water, salt and potassium replacement;

(5) Polyunsaturated oil, 2 to 8 tablespoons a day as tolerated to decrease uptake of toxins in the intestine and facilitate their excretion;

(6) Calcium and magnesium supplements;

(7) A daily routine of exercise and sauna for a period of several weeks, balanced meals, adequate rest and no drugs, alcohol or medications.

This approach is not considered a "cure" but is claimed to facilitate the recovery of certain patients with multiple chemical sensitivities. Randolph cites several cases in which significant improvement in patients' food and chemical sensitivities have occurred. Randolph states:

> "The task of defining the relationship between exogenous and endogenous chemicals in particular patients remains. At this time, we can say that reducing endogenous accumulations of toxic chemicals appears vitally important to the effective treatment of some environmentally ill patients; and the development of a safe and effective method for reducing these burdens gives us a welcome new tool for treatment." [Randolph 1980]

Clearly, these trials need to be replicated. The mass balance of chemicals must be tracked carefully to be sure that chemicals are not migrating to other parts of the body and that they are being excreted.

3. Vitamin and Mineral Supplementation

There are much data now to indicate that vitamins and minerals influence the toxicity of environmental incitants. Amino acids and fat content of the diet also may be important. For example, vitamin E deficiency increases ozone toxicity in rats. An awareness of the role of nutrition in allergy is also developing. Low vitamin B_6 concentrations have been found in adult asthmatics and supplementation with B_6 produced a dramatic drop in the frequency and severity of wheezing or asthma attacks [Reynolds 1985]. Another recent paper reports significant improvement in atopic dermatitis with vitamin C supplementation [Kline 1989].

Rea and other clinical ecologists routinely measure vitamin and mineral levels in their patients with chemical sensitivities [Johnson 1989] and supplement as indicated. In a sample of 118 patients studied in the Environmental Control Unit in Dallas, mineral levels outside the normal range were found in 53% (higher than normal) of the patients for magnesium, 88% (lower than normal) for chromium, and 47% (higher than normal) for aluminum [Johnson 1989]. A number of abnormal vitamin levels were also found. In some cases, testing for deficiencies involves more than a routine blood test; Rea feels that red blood cell and plasma magnesium levels are poor indicators and prefers an intravenous magnesium challenge to assess magnesium status [Rea 1986b]. When ecologists recommend nutritional supplements for their patients, most exercise extreme caution to avoid vitamins derived from food sources that might trigger symptoms, e.g., vitamin C from sago palm may be substituted for the usual commercial vitamin C preparations which often contain corn. McLellan cautions that before nutritional therapies are embraced too quickly, one must recognize there is a lack of human data and that most available research pertains to the interaction between single nutrients and single toxins in relatively high doses in contrast to the mixed exposures at lower levels encountered by the patient with multiple chemical sensitivities [McLellan 1987]. However, nutritional status is relatively easy to measure and supplementation can be done fairly safely. There is at least a theoretical basis for using supplements. Animal and human research have supported use of antioxidants, vitamins A, C, E, and selenium to protect against certain pollutants [Calabrese 1978; Shakman 1974]. Such antioxidants may prevent free radical production that could trigger synthesis of inflammatory prostaglandins [Metz 1981].

Galland [1987] reports several nutritional abnormalities in his chemically sensitive patients, most notably decreased excretion of essential amino acids in 40% despite a high protein diet. Erythrocyte superoxide dismutase activity was decreased in 89% (24 patients) versus 79% (15) in allergic controls (not significant); erythrocyte

glutathione peroxidase activity was decreased in 48% (11) versus 36% (5) allergic controls (not significant). One could argue that some of Galland's controls might have been misclassified since all had either allergies or somatic complaints such as fatigue. Nevertheless, Galland reports that supplementation with anti-oxidants, including selenium, copper, zinc, and sulfur-containing amino acids, produced major clinical improvement in 25% (14) of chemically sensitive patients.

An enormous number of other therapies too numerous to mention have been invoked by clinical ecologists and others. These include dietary, neutralization, and pharmaceutical treatments for candidiasis (indeed, some traditional allergists mentioned they found nystatin beneficial in treating certain patients for systemic candidiasis and they wished there were more data to help evaluate this); acupuncture; pancreatic enzymes for food intolerance; oral sodium cromoglycate for food intolerance; transfer factor; and other therapies. It is outside the scope of this report to discuss these; however, it is clear that a host of therapies, many of which have been severely criticized for being "unproven," are being offered to patients with multiple chemical sensitivities in an effort to improve their outcome. Some patients report that they obtain small increments of benefit, occasionally more, from each intervention, but none is curative.

For the patient who is having an acute reaction to an environmental incitant or food, there are certain "first aid" treatments recommended by ecologists. In the event of an acute reaction, particularly to a food, some patients take baking soda or a combination of sodium bicarbonate, potassium bicarbonate and calcium carbonate with water (so-called "tri-salts"). They claim these measures relieve their symptoms within moments. Critics caution there may be dangers in using such treatments indiscriminately, e.g. as the treatment for IgE-mediated food anaphylaxis. The ecologists' rationale for this therapy, which patients claim can be quite effective acutely, was discussed in Section VA. Powdered vitamin C in water is used by some to mitigate a reaction. In severe cases, some ecologists administer bicarbonate or vitamin C intravenously, for example, to stop a seizure resulting from a food or chemical challenge. Administration of oxygen has also been used in severe reactions. Randolph examined scleral blood vessels of patients before, during and after reactions to foods and noted increased sludging of red cells; he reasoned that such clumps decreased the red blood cells' ability to carry oxygen. Others have criticized the use of oxygen in these patients without first obtaining a blood oxygen level [Terr 1986]. However, oxygen is accepted by many as an effective drug for certain medical conditions, even in cases where there is a normal blood oxygen level. The manner in which these treatments are administered to patients is likewise important. Fresh plastic tubing commonly used for oxygen and intravenous lines may leach small amounts of plasticizers, provoking severe symptoms in some chemically sensitive patients.

In summary, clinical ecologists employ a wide variety of treatments, some unproven, in their efforts to help their chemically sensitive patients. When first used, any medical therapy is experimental. It can be argued that patients with disabling diseases demand and deserve the opportunity to try new, albeit unproven, treatments

provided these do not result in serious harm. It must be remembered that even conventional immunotherapy, used by traditional allergists, is not without hazard: over the past 39 years, at least 46 deaths have occurred during conventional allergy shots or skin testing [Lockey 1987].

It is important to keep arguments concerning ecologic therapies in perspective. Salvaggio, an allergist, reflected upon the role of unproven therapies in medicine:

> "The practice of medicine will, to be sure, remain primarily an art rather than a science, and physicians will of necessity continue to use clinical judgment and weigh benefit/risk ratios in prescribing a large number of therapeutic procedures that have not been proved to be efficacious by controlled studies. Indeed, one could fill several pages with a list of commonly employed therapeutic procedures in all fields of medicine that have not been proved to be efficacious." [Salvaggio 1981]

VI. AREAS OF AGREEMENT AND DISAGREEMENT BETWEEN ALLERGISTS AND CLINICAL ECOLOGISTS

On the basis of interviews with key individuals in allergy, clinical ecology and occupational medicine, and on the basis of the literature we reviewed, we have discovered both areas of common ground regarding the chemically sensitive patient and areas of disagreement. While some of the tension between allergists and clinical ecologists may stem from a competition for patients, there are also more fundamental differences in scientific/medical viewpoints. All physicians agree that chemical exposure can be harmful to any and all systems of the body. Disagreements exist as to what levels of exposure are necessary to cause health effects, what particular symptoms or diseases are associated with specific chemical exposures, and what mechanisms of causation come into play. There is a wide range of opinion as to the extent to which the problems of the chemically sensitive patient are psychiatric in origin.

Physicians we interviewed concurred that isolation of the patient in an appropriate environmental unit away from chemical substances in food, air and water is essential to unravelling the myriad substances that may be causing a variety of effects. More specifically, all of the traditional allergists with whom we spoke acknowledged that in the study or workup of patients with possible environmentally-induced disease, attention must be paid to the possible role of adaptation. Low-level exposure to chemicals must be avoided prior to testing patients for chemical sensitivities in order to avoid adaptation and the loss of a measurable effect. All allergists acknowledged the necessity of controlling for adaptation in any rigorous study of chemical sensitivity, as has been done in the study of ozone (see Section IVA(2)). Further, all agreed that an environmental unit such as that formerly operated by Dr. Selner in Denver would be an important tool for future investigation and understanding of chemical sensitivities.

Some allergists tend to favor psychiatric referral for patients who do not improve, while clinical ecologists are of the opinion that the patients' problems, although difficult to solve, are nonetheless likely to be physical in nature. Ecologists feel that environmental factors must be carefully excluded (i.e., in a unit if necessary) prior to invoking psychiatric diagnoses.

All physicians agree there is a need for studies to clarify unproven therapies, and some physicians in both allergy and clinical ecology think it would be best if they worked together to design the necessary protocols, conduct the studies, and evaluate the results. A few allergists are embracing the fundamentals of clinical ecology such as adaptation and avoidance, but decline to identify their views with those of the clinical ecologists. Allergists have been openly hostile to clinical ecology in the past [JACI 1980, 1981, 1986]. However, recently there has been a marked shift in the attitudes of some physicians, who are tired of name calling and legal entanglement, which they recognize as contrary to their patients' best interests. Increasingly, they want to air and resolve their differences and identify avenues of cooperation. For a

fuller understanding of the differences in viewpoints between allergists and clinical ecologists, the reader is referred to the article written by Bell [Bell 1987b] and the position paper on clinical ecology written for the American College of Physicians by Terr [American College of Physicians 1989].

PART THREE

VII. RESEARCH NEEDS

> "...the time has come to give the study of the responses that the living organism makes to its environment the same dignity and support which is being given at present to the study of the component parts of the organism...exclusive emphasis on the reductionist approach will otherwise lead biology and medicine into blind alleys." [Rene Dubos]

Earlier sections of this report focused on the magnitude and nature of the chemical sensitivity problem, possible mechanisms, diagnostic approaches, and therapies. These sections addressed various issues from the perspective of an individual patient, or, perhaps more correctly, from the perspective of a physician-scientist looking at individual patients. It might seem that a problem with such a variety of possible causes and multitude of possible effects would be hopelessly complex to sort out, but in a very real sense it is the complexity and multifactorial nature of the problem that may contribute to its clarification.

Patients with chemical sensitivity differ among themselves and present themselves differently to different physicians. It appears that the diagnosis a patient receives depends in a very real sense upon which physician's door he/she enters. It may also be that very different people enter particular physicians' doors, manifesting a referral and selection bias. For example, Dr. Rea sees individual referrals from other physicians and self-referred patients, 20% of whom go on disability while Dr. Terr published data on patients referred to him for evaluation, mostly for compensation purposes. Physicians seeing patients with problems stemming from tight buildings or industrial workplaces may see still different groups of affected individuals. This results in the proverbial blind man and the elephant problem.

An important research goal is not only the accurate characterization of symptoms and their relationship to specific chemicals, but, more fundamentally, characterization of the various populations or groups that appear to be chemically sensitive. We have attempted a preliminary categorization in Table VIII. Refinement of this categorization is essential and must be the first step in sorting out the myriad chemically-caused sensitivities, some of which may represent classical toxicity, some classical allergy, and some what we term multiple chemical sensitivities.

There appear to be four rather distinct groups of patients. They are:

(1) industrial workers;

(2) workers and school children in so-called tight buildings;

(3) members of communities exposed to air and water pollution from toxic waste dumps, aerial pesticide spraying, groundwater contamination, or other industrial exposures; and

Table VIII

SPECTRUM OF MULTIPLE

	INDUSTRIAL EXPOSURES	TIGHT BUILDINGS
RECOGNITION OF PROBLEM	Workers themselves; unions; occupational health clinics	Office or school workers themselves, parents of school children, school nurses
PLACE OF DIAGNOSIS	Occupational health clinic; private physician's office	Private physician's office; occupational health clinic
NATURE OF EXPOSURE	Industrial chemicals; acute or chronic exposure	Off-gassing from construction materials, office equipment, or supplies; tobacco smoke; inadequate ventilation
DEMOGRAPHICS; AWARENESS	Primarily males, blue-collar, 20's to 60's; conscious of classical workplace hazards; often aware of relationship between symptoms and exposure (e.g. better on weekends/vacations, worse at times of peak production or during certain processes, etc.). Awareness via word of mouth, union, occupational physician	Females more than males; children; white-collar office workers and professionals; 20's to 60's; aware of symptoms associated with change in building environment, e.g. new construction, carpeting or seasonal illness. Awareness via word of mouth, media, field study
MANIFESTATIONS	Multiple symptoms involving multiple systems with marked variability in type and degree of symptoms. CNS symptoms common. Physical exam most often unremarkable	Multiple symptoms involving multiple systems with marked variability in type and degree of symptoms. CNS symptoms common. Physical exam most often unremarkable. Many have symptoms of eye, nose, throat irritation
AVERAGE SEVERITY OF ILLNESS\ DISABILITY* (varies greatly with individual)	Moderate to severe	Mild

* Those individuals whose symptoms are most persistent and disabling often see a series of physicians before they finally see an ecologist. Rea's clinic represents a kind of tertiary referral system for ecologists who send him the most severe cases. Thus the patients Rea sees are markedly different, i.e., more disabled, than the typical patient seen by an allergist.

CHEMICAL SENSITIVITIES

COMMUNITY-BASED AIR AND WATER POLLUTION	INDIVIDUAL EXPOSURES
Individuals in community; government-sponsored field surveys	Individuals themselves
Private physician's office; state-supported clinical study	Private physician's office
Toxic waste dumps, aerial pesticide spraying, ground water contamination, air contamination by nearby industry, and other community exposures	Heterogeneous, personal; indoor air (domestic), consumer products, pesticide use
All ages, males and females; children/infants may be affected first/most; middle to lower class; community awareness via word of mouth, community action groups, media, or field study	70-80% females; 50% in 30 to 50 age bracket [Johnson 1989]; white; middle class, upper middle class and professionals; farmers; awareness via word of mouth, patient groups, physicians
Multiple symptoms involving multiple systems with marked variability in type and degree of symptoms. CNS symptoms common. Physical exam most often unremarkable.	Multiple symptoms involving multiple systems with marked variability in type and degree of symptoms. CNS symptoms common. Physical exam most often unremarkable
Mild to moderate	Mild to moderate if referred to allergists or clinical ecologists Severe if seen by Rea in Dallas Disabling if admitted to environmental unit or an applicant for worker' compensation or disability

(4) a heterogenous collection of individuals whose exposure may come from domestic indoor air, consumer products, pesticide use or other personal contact.

As the description of the patient demographics in Table VIII reveals, these patients often may differ greatly in employment or professional characteristics, socioeconomic status, sex, and age. They are also likely to see very different categories of physicians. Industrial workers are much more likely to see occupational physicians or private physicians. The sickest workers are more likely eventually to consult clinical ecologists. Individuals suffering from sick building syndrome are not as likely to seek out or be referred to clinical ecologists, even though they are conscious of the fact that their problems stem from tight buildings. People in polluted communities may find themselves going from physician to physician before seeing a clinical ecologist who then may determine that their problems are related to chemicals. By the time these individuals see the ecologist, they may be frustrated, angry and confused. Finally, the host of other individuals whose exposure to chemicals comes from domestic indoor air, consumer products, pesticide use etc., may vary greatly in the type and the seriousness of their symptoms and are likely to have seen a series of physicians including allergists and clinical ecologists. The most difficult patients encountered by the clinical ecologists and some allergists, those patients who are the sickest, may ultimately be referred to Dr. Rea. Rea often sees the patients who are most seriously afflicted and whose condition therefore may be less reversible. He also probably sees a greater diversity of persons with chemical sensitivities than are represented in the other three groups discussed above. In contrast, those allergists who see chemically sensitive patients referrred for worker's compensation evaluation may view only a small segment of the most ill patients.

Multiple chemical sensitivities thus encompass a broad spectrum of persons. The allergist either sees them because the patients believe they have an "allergy" or because they are referred by insurance companies or employers for workers' compensation purposes. Which physicians see which patients seems to affect greatly the acceptability of their problem as a bona fide physical illness, or at least not a problem of psychiatric origin. Relatively few physicians today would call persons who are affected by tight buildings hypochondriacal. Most workers with chemical sensitivities seek workers' compensation as a matter of last resort. They would prefer to be able to work [Davis 1989].

The above discussion illustrates the need to characterize accurately the exposure-patient profile of people suffering from chemical sensitivities in order to fashion an appropriate response. The categorization may also be useful in suggesting areas of research which might be undertaken by the federal government including the National Institute for Occupational Safety and Health (NIOSH), the National Institute of Environmental Health Sciences (NIEHS), the Environmental Protection Agency (EPA), and the Agency for Toxic Substances and Disease Registries (ATSDR). The latter agency is concerned especially with community-based pollution related to toxic waste facilities and contamination of water supplies. ATSDR has cooperative agreements with eleven states to undertake surveillance studies in contaminated

communities for exposure and disease. In addition to the federal effort, state-based efforts, usually involving state departments of health and possibly state departments of environmental protection, need to be encouraged. In the event that the federal government is not willing to undertake broad-based research as to both the nature and the etiologies of chemical sensitivity disorders, a multi-state effort may be well advised.

Most scientific criticisms of clinical ecology have been directed toward the efficacy of provocation-neutralization therapies. To focus initial research efforts in this area would be of limited value since most traditional practitioners question the diagnosis itself. Clinical ecologists must continue to develop objective means of measuring symptoms and relating them to exposures.

A properly constructed environmental health unit could serve as a focal point for studying chemically sensitive patients in the de-adapted or unmasked state. Allergists, clinical ecologists, and toxicologists should contribute to the design of any such study to ensure acceptance of the results. The unit should be contructed and operated following the highest academic standards. For reasons discussed in Section III, epidemiologic studies on chemically sensitive populations have to be done with extreme care as to study design, or no evidence will emerge at statistically significant levels. The study group must be appropriately defined and more than one symptom may need to be counted as a health effect.

Given clinical ecology's low status and reputation in the scientific community at the present time, there are serious disincentives for independent researchers to examine its tenets. Yet a critical and unbiased airing of the problem of chemical sensitivities is needed. All aspects of the problem need attention--from documentation of the sensitivity itself to diagnostic approaches for its discovery to the range of possible therapies. The National Academy of Science Panel on the Interrelationships of Toxic Exposures and Immune Response should be encouraged to study the problems of multiple chemical sensitivities as well as problems of immune system damage or dysfunction.

Government and university scientists must be allowed and even encouraged (by grants) to participate in research in this field without being hamstrung by the opinions of traditional medical practitioners. It does not serve science to continue to deny the probable existence of the problem in the face of massive and growing circumstantial evidence, though admittedly subjective in many respects. It would be better to acknowledge that something appears to be going on, observing that low levels of chemicals can affect the body in subtle ways which currently escape our understanding.

The widely-circulated journals representing traditional medicine must also allow unbiased airing of this problem, as they have with other issues, e.g., medical versus surgical treatment of coronary artery disease. There are a number of university and government scientists who are knowledgeable about chemical sensitivity and who feel it is worth taking seriously. However, many fear for their own professional careers and are reluctant to write or speak openly on the subject. Debate, not

unilateral criticisms of unproven ideas, is what is needed to encourage or make possible defensible research on these ideas. Certainly, criticisms of therapies should not be used to foster a denial of the existence of chemical sensitivity altogether. Recently there appears to be a willingness on the part of physicians and scientists to accept the concept of chemical sensitivity in the context of occupational exposures or tight buildings. Perhaps because most patients suffering from these exposures do not seek clinical ecologists, mainstream physicians are probably more accepting of the problems in those contexts. If clinical ecologists are involved, there seems to be more of a desire to shoot the messenger than take the problem seriously. As similarities are recognized among patients whose exposures arise in different contexts, hopefully a more scrutinizing evaluation will be forthcoming.

VIII. PATIENT AND COMMUNITY CONCERNS

In this section of the report we articulate the concerns and needs of the chemically sensitive patient or person, and the needs of the community in preventing illness triggered by or associated with low-level exposures to chemicals. These needs include information; health care; alternative schooling, employment and housing; medical insurance; compensation for disability; social and legal services; and the control of chemicals in the office, industrial workplace, home and consumer products.

A. Information

1. Information Regarding Chemical Sensitivity

Chemically sensitive persons need information and guidance concerning the recognition of chemical sensitivity and the availability of diagnostic tools and possibly effective therapies. They need to understand that chemicals can cause both classically recognized environmental/occupational disease (such as lead or solvent poisoning, or allergic reactions to organic dust) and less well-understood, but nonetheless real, problems associated with low-level exposures. Industrial workplaces can give rise to both kinds of environmental illness, and it may be especially difficult to unravel the vagaries of causation there. Home and office environments also present a mixed bag of illnesses, perhaps more often characterized by lower level exposures. Episodic exposures to chemicals present still different challenges. Chemically sensitive persons need assistance in understanding their condition so that they can make reasoned choices about the health care or preventive actions they might pursue.

2. Information Regarding Chemicals

Chemically sensitive patients need to know the potential hazards of the chemicals they work with or may be exposed to. Federal and state right-to-know legislation and SARA Title III reporting requirements are important legal avenues for information held by government agencies, employers, and manufacturers/producers. However, patients may need more specific information necessitating industrial hygiene surveys by OSHA or state agencies, or possibly by insurance carriers. Access for individuals to a central state source for information and services is needed.

B. Health Care

1. Access to Appropriate Care from Private Physicians and Clinics

In one profile of chemically sensitive patients seen at a clinical ecology clinic, 30% of the patients had seen 6-10 physicians before coming to the unit [Johnson 1989]. Brodsky observes:

> "Many of these patients shift from one specialist to another, going from family physicians to allergists to neurologists and other medical specialists, and to chiropractors, acupuncturists, homeopaths, and even faith healers. Both the patients and their physicians feel frustrated and dissatisfied, the patients because they remain convinced that their symptoms signal a physical disorder for which a medical explanation must exist and the physicians because they have been impotent as healers, unable to help these obviously distressed individuals or to reassure them that they do not have a serious disease. Such patients are time-consuming and in clinic settings not infrequently objects of derision." [Brodsky 1987, 695]

From our investigations, it is clear that the chemically sensitive patient finds medical care by trial and error and by word of mouth. A more directed path and identification of helpful physicians and clinics is needed. Patients whose problems stem from occupational, sick building, or home environments may each need different care, as might persons suffering from episodic exposures. No sensible referral system exists, and the segmented nature of medical care and the inability of some physicians to acknowledge a disease they do not understand contributes to the personal suffering of the sometimes bewildered patient. Multi-specialty clinics, HMO's, and PPO's, unfortunately rarely include specialists in diseases caused by chemicals. Occupational medicine clinics have the potential for expanding their concerns and services into illnesses caused by low-level exposures, but specific initiatives are needed to bring this about. Taking work and/or environmental histories is essential to delivering appropriate medical care. Industrial hygiene services in both the home and workplace may also be indispensable.

University-based clinics, such as those at the Robert Wood Johnson Medical School, have the potential for rapidly incorporating new knowledge and perspectives more quickly for the recognition, diagnosis and treatment of the chemically sensitive patient. The potential needs to be realized, however.

2. Avoidance

The first line of defense for the chemically sensitive patient is the avoidance of offending chemicals and substances found or suspected to cause problems. Some kinds of avoidance are easy, but others are very difficult. Persons suffering from sick building illness may have to abandon employment or residence in those buildings. In the case of children who are chemically sensitive, an alternative to home tutoring may be the state provision of environmentally "safe" classrooms where students with documented and suspected chemically-related disorders could be educated and observed for follow-up. This practice is currently being pursued in Canada [Rapp 1986]. In Maryland's guidelines for indoor air quality in schools, modification of workplace exposure limits is recommended [Maryland 1987, 6].

C. Alternative Employment and Housing

1. Alternative Employment

Federal and state laws require that employers provide handicapped workers reasonable accommodation in retaining employment. Deciding whether a chemically sensitive person is handicapped is done on a case-by-case basis. In some instances, work at home may be possible. (EPA seems to have reached this accommodation with some of its chemically sensitive employees [Hirzy 1989b].) If the patient is not considered handicapped, he/she nonetheless has the need for rehabilitation and for return to gainful employment.

2. Alternative Housing

Some chemically sensitive patients can not live in their prior domiciles. This may have severe economic consequences. Some assistance is obviously needed. Options include "half way" houses for the severely affected and the establishment of experimental communities in non-polluted areas.

D. Medical Insurance

It is becoming increasingly difficult for patients to receive reimbursement for medical expenses incurred when the diagnosis and treatment of chemical sensitivity is performed by clinical ecologists [Davis 1989]. Even though a prominent allergist and critic of clinical ecology, Dr. Abba Terr, has stated that "what we do is as unproven as some of the things we are criticizing" [Terr 1988b], allergists have

organized letter-writing campaigns to urge the Health Care Financing Administration (HCFA) to deny reimbursement for "unproven" techniques. Such efforts do not seem to deter the desperate patient from seeking medical care; it just makes the patient more desperate. Recognition of diagnosis and treatment of chemical sensitivity for insurance purposes is necessary on both grounds of fairness, and in the case of some patients, to enable them to receive adequate care. For traditional medical practitioners to throw up their hands and not be able to help these patients and, at the same time, to lobby vigorously to deny them therapies that sometimes, if not often, relieve their suffering, can not be justified.

E. Compensation

Chemically sensitive patients are sometimes unable to continue to work in a specific workplace, often an industrial workplace, or may not be able to work at all. Workers' compensation systems have been painfully slow to provide coverage for occupational diseases. Employers and their insurance carriers have historically denied the work-relatedness of disease associated with chemical exposures. Sixty percent of occupational lung disease claims are contested [U.S. Department of Labor 1980]. It is no wonder that compensation for the chemically sensitive worker is vigorously resisted. It seems unfair that in some cases the patient has to be labeled with a psychiatric disorder, e.g., post traumatic stress disorder, in order to receive compensation for a real disease. Earon Davis, an attorney and Executive Editor of the Ecological Illness Law Report believes only about 1% of severely affected chemically sensitive workers will file a workers' compensation claim because they do not want to be labeled as psychiatric cases. In addition, many workers leave jobs because of chemical sensitivity only to find themselves unable to tolerate a new job and unable to file a claim against either their new or old employer [Davis 1989].

In most instances the chemically sensitive person cannot trace his problems to a particular work-related exposure and he or she may seek disability payments under Social Security. Dr. William Rea, who sees the most severely affected patients, reports that about 20% of those he sees go on disability [Rea 1989]. In cases of illness stemming from pesticide exposure or from some other episodic exposure involving industrial or consumer products, the patient may seek compensation through a suit in tort. In 1987, the Consumer and Victims Coalition Committee of the Trial Lawyers of America adopted a resolution supporting "environmental illness" victims. Recovery of damages based on alleged immune system damage is becoming more commonplace, and the manufacturers and insurance industry are reacting vigorously. Dennis Connolly, an insurance executive, writes:

> "Courts as well as scientists are routinely grappling with the problems of harmfulness and causation. A disturbing trend from the point of view of those who might be looking toward providing insurance is the increased use of various forms of marginal science to overcome difficulties in proving causation. 'Clinical ecology' is a 'science' offering

> broad support for causation in bodily injury cases, but the science has been repudiated by many in the medical establishment and cited as an example of poor science flourishing in the courtroom." [Connolly 1988]

Academics have joined the criticism. Professor Donald Elliott writes:

> "...plaintiffs in toxic tort cases are increasingly relying on testimony by a small group of professional witnesses called 'clinical ecologists' (whose views are repudiated by the scientific establishment). Lay juries and the public are vulnerable to being mislead by such 'experts.'" [Elliott 1980]

Powerful economic and industrial forces have joined to deny the chemically sensitive patient compensation, just as they did earlier in this century for occupational injury, and later for occupational disease, accusing the worker of malingering and bad faith. The issue of compensation may seem peripheral to the scientific-medical debate over chemical sensitivity, but it is actually central to the resolution of public policy in this area. Economic issues heighten the conflicts between allergists and clinical ecologists and need to be resolved if an optimum scientific consensus is to be achieved. The existence or origins of the patients' disease are contested in conflicts over who should pay while the patient continues to suffer. Brodsky observes:

> "Private and public agencies that provide disability benefits argue that these patients are not truly disabled, although those dealing with them recognize that they are in great distress." [Brodsky 1987, 696]

F. Social and Legal Services

As with other persons debilitated by disease, chemically sensitive persons are in need of psychological, financial, and legal counseling to enable them to manage their affairs, seek help from appropriate governmental agencies, and cope with stress. Some of these services can be provided by state government and private patient support groups, such as the National Center for Environmental Health Strategies of New Jersey. Earon Davis reports that many chemically sensitive persons suffer neuropsychological defects often resulting from continuing unavoidable exposures and have extreme difficulty interfacing with the legal or social service systems. He argues that these persons need social workers, not lawyers, who can guide them into avenues that improve their situation. Such guidance could be provided at "half way" houses or special communities [Davis 1989].

G. The Regulation of Chemical Exposures and Other Preventive Initiatives

The community has an interest in preventing and limiting the problems of chemical sensitivity. For chemical sensitivity that has its origin in exposures to

chemicals in the workplace, pesticides, chemical spills, etc., adherence to and enforcement of existing environmental regulations is necessary to prevent sensitization of more individuals. The existing standards of OSHA, EPA, and state agencies do not, however, protect those individuals already sensitized. New regulations governing inadequately regulated substances or unregulated applications of chemicals, such as pesticides applied in office buildings, schools or apartment complexes, are also needed. At a minimum, regulators should require that the applications be accompanied by adequate notice so that people can avoid the exposure. Currently most OSHA and EPA regulations control exposures at the parts per million (ppm) level. More stringent regulations may be needed to protect both sensitized (and hence chemically sensitive) individuals and individuals who may become sensitized. The mandates behind environmental regulation do indeed require the protection of sensitive populations [Friedman 1981].

The appearance of similar kinds of health problems in widely divergent populations exposed to chemicals (see Table I) illustrates that the failure to adequately regulate or prevent exposures to chemicals in the environment, workplace and consumer products has resulted in the present chemically sensitive population. In order to adequately protect this population from further or continuing damage, some chemicals, such as formaldehyde, will need to be controlled at the part per billion (ppb) range or banned outright for some uses [Massachusetts 1989, 74-102]. While the regulation of chemicals traditionally has been viewed as a federal government initiative with states as secondary partners, it may be necessary for states such as New Jersey to take vigorous regulatory action in order to protect the chemically sensitive. Massachusetts, for example, banned the use of urea formaldehyde foam insulation. California regulated vinyl chloride level in ambient air even though the federal government issued only emission limitations. New Jersey may need to examine the adequacy of its regulations.

IX. THE ROLE OF MEDICAL PRACTITIONERS AND THEIR SOCIETIES

In this section we identify the potentially positive roles that primary care physicians, occupational/environmental health physicians, allergists, and clinical ecologists can play in addressing the needs of the chemically sensitive patient. The roles differ depending upon the group of patients in need. Table IX depicts the strategies that might be followed for each group of chemically sensitive patients. It would be fair to say that, at this time, patients consult clinical ecologists and allergists out of desperation, rather than as a result of referrals. It is our considered opinion that a structured, sensible referral strategy needs to be developed along the lines that we discuss below.

Primary care physicians are in the best position to provide knowledgeable referrals for chemically sensitive patients--referring them to the health professional most likely to be of help to the patient. Workers exposed to industrial chemicals should be referred to occupational health clinics or occupational physicians. The coupling of industrial hygiene services and a detailed work history help occupational physicians decide what can be done for the chemically exposed patient. In the absence of or in cooperation with an occupational physician, the industrial hygienist may aid primary care physicians in identifying possible illness and relevant exposures. If the problems that the worker is experiencing are those of classical toxicity, such as chronic lead poisoning, the occupational physician will be able to help the worker directly. In special cases, such as polybrominated biphenyls (PBB) exposure, some occupational physicians might refer the patient for detoxification therapy to remove the bio-accumulated toxins [Schnare 1986]. When the worker is seen to exhibit chemical sensitivity of a non-traditional nature, the occupational physician may be able to help the patient himself if he is knowledgeable about multiple chemical sensitivity problems. Indeed, many occupational physicians are developing their knowledge in this emerging area. Alternatively, the occupational physician may refer the patient to either a clinical ecologist in whom he has confidence or to an allergist who accepts (recognizes) the problem of multiple chemical sensitivities as real.

Occupants of tight buildings, who could be suffering from either classical sensitivity, e.g., to molds, or from multiple chemical sensitivities, can also be referred to an occupational health clinic or an occupational physician. The occupational physician may then manage the patient him/herself or provide the appropriate referral, as described above.

For patients that comprise part of a contaminated community, the primary care physician should, ideally, involve the state health department and the Environmental Protection Agency (EPA) or the Agency for Toxic Substances and Disease Registry (ATSDR) which could document exposures and watch for a pattern of illness in that community. With the assistance of these agencies, the primary care physician can make appropriate referrals to physicians expert in occupational and/or academic environmental medicine. These physicians will take an environmental history in much the same manner an occupational physician takes a work history, and this history

Table IX
STRATEGIES FOR PRIMARY CARE PROVIDERS

Group	Strategies	
	Primary Referral	Subsequent Referral
Workers	Referral to Occupational Health Physicians* or Clinics* • Work histories • Industrial hygiene surveys	• Clinical ecologists* • Allergists* • Detoxification programs*
Occupants of Tight Buildings	Adults: As above for office workers Children: Clinical ecologists* or allergists*	As above for office workers
Contaminated Communities	With help of • State health department • EPA • ATSDR** Referral to environmental/ occupational health physicians to take an environmental exposure history	• Clinical ecologists* • Allergists* • Detoxification programs*
Individuals		
Pesticides and other toxic substances	As for contaminated communities	As for contaminated communities
Indoor air (domestic)	• Clinical ecologists* • Allergists*	

* Selected with great care
** Agency for Toxic Substances and Disease Registry

needs to be coupled both with disease patterns recognized by and with exposure measurements made by the state health and environmental protection departments, EPA or ATSDR. At that point the occupational or environmental medicine physician can make appropriate referrals to clinical ecologists or allergists in whom he has confidence. There are relatively few physicians who specialize in environmental medicine. Since environmental medicine and occupational medicine have similar knowledge bases and require many of the same skills, efforts should be directed at developing professionals who span both fields in order to better serve the chemically sensitive patient. In New Jersey at the Robert Wood Johnson Medical School, the state has an excellent department of environmental medicine directed by Dr. Bernard Goldstein. Cooperation between this department and the New Jersey Department of Health would be very helpful to the chemically sensitive patient.

Finally, for the divergent group of individuals whose illness results from indoor air in the home, pesticide applications, or other chemical exposures, the primary care physician may need to find ways to identify those clinical ecologists and allergists who are able to help the chemically sensitive patient. This group of patients is most challenging because the patients are diverse and may not fit a particular pattern of illness like the patterns often seen in the workplace, in tight buildings, or as part of a contaminated community. Indeed, some of these patients may not recall a sensitizing event although they recognize chemical triggers of their symptoms and they are polysymptomatic.

The strategies we have outlined for dealing with these four groups of patients need to be carefully developed and refined. The weakest link in affording the patient proper medical care involves raising the consciousness of primary care physicians or those specialists whom the patient might see in a random manner such as ear, nose and throat specialists, neurologists, rheumatologists, and so forth. However, engaging the primary care physician is the first essential step in sending the patient down a directed pathway of proper referrals. The primary care physician's level of knowledge and concern regarding this problem must be given immediate attention.

The role of the medical specialty societies is central in facilitating the success of these referral strategies. For the primary care physicians, including those in family practice, internal medicine and pediatrics, a clear understanding of the problems of the chemically sensitive patient is requisite. For other specialists, their societies need to address the particular problems of chemical sensitivity that relate to their specialty.

The allergists need to adopt broader perspectives [Kniker 1985; Selner 1985] which several outstanding allergists seem to be doing. Selner observes:

> "[I]t is time for allergy to claim its interest in [the chemical environment] and assume a more active role in the field of toxicology. Allergy is in a position to bring the same disciplined commitment to the principles of scientific investigations to the area of chemical intolerance that has resulted in the remarkable contributions to the field of immunology over the past two decades." [Selner 1985b, 666]

The allergy societies need to commit themselves to a critical but fair appraisal of those techniques and approaches of clinical ecology that may be useful in expanding the practice of allergy beyond its present boundaries. Selner, for example, has stressed the importance of an environmental care unit [Selner, 1985a]. Allergists need to be able to take comprehensive work and environmental histories, to learn about toxicity and chemical sensitivity, and to familiarize themselves with appropriate diagnostic and therapeutic approaches and techniques. Bardana and Montanaro, for example, have suggested that industrial hygiene evaluations of both the workplace and the home "may prove invaluable in identifying chemical sensitivity" [Bardana 1989]. The allergy societies should promote the practice of allergy with a broader vision. This can be done through continuing education efforts and by trying to build on common ground shared with clinical ecology and occupational medicine. Doris Rapp, a board-certified practicing allergist for 18 years and also a clinical ecologist, in response to the position papers of American Academy of Allergy and Immunology on clinical ecology, cautions:

> "[t]ry not to wedge the academy in a corner with statements that will haunt allergy in the years to come. If the thinking, leading allergists do not listen, [then] soon, the whole specialty of allergy will be lost. Use your mighty caches of money, and brains to help elucidate our impressive observations and successes. Help us refine what we are doing. Not only will you gain, but the patients, who should be the bottom line of whatever we discuss, will be helped." [Rapp 1985]

The clinical ecologists also need to learn to take better work and environmental histories; to be thorough in order to avoid overlooking other concomitant medical conditions, e.g., hypomagnesemia resulting from a prior partial gastrectomy [Bardana 1989]; to engage in continuing educational activities in this rapidly developing area; and to put their work and techniques into a form that would serve as a useful primer for others. The environmental unit is an essential tool for both allergists and clinical ecologists and their knowledge should be combined in developing new units. The societies whose members practice clinical ecology need to develop rigorous standards for its practices and shun mystical approaches. Bell concludes:

> "Clinical ecology thus needs well-designed, systems-oriented, rigorous interdisciplinary studies. The work must focus on specific diagnostic subgroupings and syndromes as well as on specific immunological and physiological concomitants of adverse reactions. Clinical ecology needs the input of scientists and clinicians from many fields such as public health, occupational medicine, and behavioral medicine, to refine its concepts, treatments, and goals. It otherwise runs the risk of extinction as a fad with several good ideas mingled with too many pernicious and unsubstantiated beliefs." [Bell 1987a]

Finally, clinical ecologists should not simply invoke traditional toxicity as a way of legitimizing the case for avoiding chemical exposures. It seems that mechanisms for multiple chemical sensitivities may be different. While it is understandable that there is pressure on clinical ecologists to come up with the theory of causation, reliance on classical toxicity or allergy may be misplaced.

X. RECOMMENDATIONS

Having identified the needs of the chemically sensitive person and the community concerned with preventing an increase in the number of chemically affected individuals, we here turn to specific recommendations for New Jersey.

A. Research

(1a) The New Jersey Department of Health should establish a registry of chemically sensitive persons with the help of physicians, industrial hygienists, labor organizations, patient support groups and others. The purpose of the registry is to characterize the nature of the problem and trends over time, and to provide a basis for linkage to geographical information system analysis at some time in the future in order to discover sources of exposure.

(1b) The State of New Jersey should provide funding for a statistically useful questionnaire survey of these persons, stratifying respondents by group, e.g., occupationally exposed, occupants of tight buildings, members of contaminated communities, etc., and if possible, by the kind of exposure thought to be responsible for the person's condition, e.g., new carpeting, pesticides, etc.

(1c) The State of New Jersey should solicit the financial support of health insurance companies doing business in the state for this effort.

(1d) The New Jersey Department of Health should analyze the results of the survey in order to identify problem chemicals and affected groups that might serve as the focus for specific field studies.

(2) With the assistance of ATSDR, the New Jersey Department of Health should undertake field studies of various subgroups of chemically sensitized persons identified in (1d) above to document their illness. The groups should include occupational groups, contaminated communities, office workers and children. Studies should involve incidents where exposures have led to recognized problems, such as certain workplace exposures, toxic waste dumps and tight buildings.

(3) The New Jersey Department of Health should request the federal agencies, NIH, NIEHS, EPA and ATSDR, to construct a patient profile of those with chemical sensitivity by evaluating the Environmental Health Center in Dallas. Dr. William Rea has agreed in principle to such a study.

(4) The New Jersey Department of Health should press for a national conference to identify key areas for research into chemical sensitivity that might be undertaken by NIH, NIEHS, EPA, NIOSH and ATSDR. Allergists, immunologists,

clinical ecologists and occupational/environmental physicians should participate as well as key governmental researchers.

(5) The New Jersey Department of Health should create an inter-agency working group of state agency professionals to guide the development of the state initiatives relevant to the problems of chemical sensitivity.

B. Information

(1) The New Jersey Department of Health should designate [a] professional[s] to staff a three-year effort addressing low-level exposures to chemicals. The designated professional (and necessary support staff) should be responsible for preparing written guidelines for the chemically sensitive person designed to assist the affected individual by providing him with a clear understanding of his condition and his options for diagnosis, treatment and compensation. The New Jersey Department of Health should provide a telephone "hot line" for the chemically sensitive person in order to guide his inquiries to the appropriate state agencies and offices.

(2) The New Jersey Department of Health should request the Robert Wood Johnson Medical Center to identify, compile, and maintain a list of physicians and clinics interested in handling the chemically sensitive patients with consideration, understanding and relevant medical or other interventions.

(3) The New Jersey Department of Health should prepare educational materials and hold short courses in conjunction with local medical associations giving guidance to primary care physicians in the recognition, diagnosis, treatment and referral options relevant to chemical sensitivity. Details of possible referral strategies were discussed in Section IX of this report.

(4) The New Jersey Department of Community Affairs, with the cooperation of the Departments of Health and Environmental Protection, should convene a meeting of those concerned with the design and construction of public and private office buildings to inform them of the problems of indoor air pollution.

C. Health Care

(1) The New Jersey Department of Health should seek state funds to enhance the capabilities of existing occupational health clinics to address problems of chemical sensitivity through financial and professional support.

(2) The New Jersey Department of Health should encourage the insurance carriers to provide industrial hygiene services for homes, and workplaces where

multiple chemical sensitivities are suspected. Schools, where problems are indicated, should be investigated by the State.

(3) The New Jersey Department of Health should seek state funds to establish a pilot or demonstration environmental health unit at the Robert Wood Johnson Medical School, assisted by those experienced in establishing and operating a successful unit.

(4) The New Jersey Department of Health should encourage the Department of Education to evaluate the size of the problem among school children and to consider establishing [a] special classroom[s] for chemically sensitive children. These special classrooms should be used to study and document the impact of avoidance measures for this subpopulation.

D. Alternative Employment and Housing

(1) The State of New Jersey should educate employers about the chemically sensitive and encourage employers to provide alternative worksites within their places of employment, and in some cases, to allow employees to work at home while they improve. The state should also inform employers and employees of their obligations and rights under federal and state legislation for the handicapped.

(2) Vocational rehabilitation programs should be established for the chemically sensitive worker, coordinated with programs and activities of the State Department of Labor and Workers' Compensation Board.

(3) The working group established by recommendation A-5 above, should be convened to coordinate efforts related to alternative employment discussed above and to study housing needs. One option to be studied should be the establishment of "half way" houses where newly diagnosed persons or less severely affected persons can recover and receive guidance. Options for the establishment of experimental communities in less polluted environments should also be seriously investigated.

E. Medical Insurance

(1) The New Jersey Departments of Health and Insurance should undertake a study of economic savings that might result from timely and effective medical intervention for chemically sensitive persons.

The New Jersey Department of Health and Department of Insurance should use their good offices to express their disapproval of attempts to curb reimbursement for health care for chemically sensitive patients. This effort should be directed towards HCFA, Blue Cross/Blue Shield and other health insurance carriers. As the

problems of the chemically sensitive become better understood, the state should do all within its power to facilitate recognition of chemical sensitivity for both health insurance and disability purposes.

F. Compensation

The New Jersey Department of Health should convene a meeting with the Department of Insurance and the New Jersey Workers' Compensation Board to explain the work-relatedness of chemical sensitivity.

G. Social and Legal Services

The working group created by recommendation A-5 should study the state's options for providing access to medically related social and legal services to persons whose illness stems from chemical sensitivity.

H. Regulation of Chemicals

The New Jersey Department of Health, in conjunction with the New Jersey Department of Environmental Protection and New Jersey Department of Labor, should consider revising or adding state standards to deal with low-level exposure to chemicals in the environment, industrial workplace and office and consumer products. New ventilation standards currently under consideration for public buildings is one example of desireable preventative measures. Just as "no smoking" areas are provided in public and private facilities, environmentally acceptable areas could be required. The state should work closely with the U.S. Environmental Protection Agency's Office of Indoor Air Pollution to establish federal policy for chemical sensitivity.

I. Resolution of Conflicts Among Medical Practitioners and their Societies

1. The New Jersey Department of Health should facilitate dialogue and an easing of antagonisms among allergists, clinical ecologists and occupational/environmental physicians through educational efforts (see Recommendation B-3) and through co-sponsorship of conferences on chemical sensitivity (see Recommendation A-4).

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APPENDIX A.

LIST OF PERSONS CONTACTED OR INTERVIEWED

Bardana, Emil
Bell, Iris
Bresnitz, Eddy
Cullen, Mark
Davidoff, Linda Lee
Davis, Earon
Gerdes, Kenneth
Hirzy, Bill
Jewett, Donald
Johnson, Alfred
King, William
Kniker, William T.
Lamielle, Mary
Levin, Alan
Meggs, William
Metcalfe, Dean
Miller, Joseph
Ozonoff, David
Patients
Randolph, Theron
Rapp, Doris
Rea, William
Salvaggio, John
Selner, John
Slavin, Ray
Teich, Morton
Terr, Abba
Wallace, Lance
Welch, Laura
Ziem, Grace

APPENDIX B

EXTERNAL PEER REVIEW

The New Jersey State Department of Health has a policy of submitting all internally and externally generated public reports for external peer review prior to public release. Peer review panel members are selected to represent expert opinions from all fields, disciplines, and view points related to the topic of the report.

The external peer review panel for this report consisted of the individuals listed below. Due to the diverse and extensive nature of comments submitted by the reviewers of this report, highlights of the reviewers' comments are provided on the following pages.

Expert External Peer Review Panel for Chemical Sensitivity: A Report To The New Jersey Department of Health prepared by Nicholas A. Ashford, Ph.D., J.D., and Claudia S. Miller, M.D., M.S.

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GOALS

In writing this report, the goals of the authors were to: (1) clarify the nature of chemical sensitivity, and (2) identify ways in which a state department of health could address the chemical sensitivity issue. Most reviewers agreed that the authors conducted extensive research and provided a detailed discussion of the issue. Although the reviewers did not all agree with the document in its entirety, the general opinion was that the authors met their goals.

OBJECTIVITY OF THE REPORT

Opinions varied as to the objectivity of the material presented by the authors. The need for data on control populations for comparison was noted by several reviewers. Some reviewers stated that the report could have been more objective if a scientific critique of clinical ecology were included in the report, thereby giving more strength to the points that the authors were trying to make. One reviewer stated that the language used sometimes conveyed a tone of non-objectivity and that modification of certain words or phrases may help to present a more balanced tone to the document. Other reviewers expressed general satisfaction with the report -- that it was well researched, balanced, and complete.

DEFINITION OF CHEMICAL SENSITIVITY (CS)

Several reviewers were not satisfied with the operational definition of CS provided by the authors in the report. Although the reviewers did not offer an alternate definition, some agreed that the definition needed to be one that was a consensus of opinion from all clinical perspectives and that perhaps an operational definition may not be the best choice.

SCOPE OF CS

Some reviewers expressed the need for data delineating the numbers and demographics of the population affected. Without a clear understanding of the scope of the problem, the reviewers said, it is not possible to fully examine the feasibility of the recommendations that the authors offered. The scope of the problem is dependent upon the definition of CS as several reviewers pointed out.

DIAGNOSIS AND TREATMENT

Many reviewers expressed concern over the emphasis that the authors placed upon the environmental unit for diagnostic and treatment purposes. Although nearly all the reviewers agreed that environmental units would be necessary to learn more about what substances were linked to environmentally-involved illness in sensitive individuals, there was a lot of concern expressed over how such units would be implemented. The major concerns expressed by the reviewers include the following:

1. A screening process would need to be established with clear parameters as to who would be eligible to enter such a unit and who would be excluded. It was recommended that those individuals with pre-disposing medical conditions that would not permit the fasting period be excluded.

2. Exposing patients to minute amounts of various substances to test reactivity and sensitivity may be a hazard in and of itself. There are serious ethical issues involved in deliberately exposing individuals to potentially hazardous substances.

3. Such units would have to include the double-blind testing of subjects in a way that would report symptoms without bias.

4. There is no information provided as to how "normal" or "control" populations respond to the environmental unit. It is possible that the experience of going through the "clean" unit may affect the reporting of symptoms upon removal from that environment.

Although the authors pointed out that the Provocation-Neutralization therapeutic approach is an evolving technique and that its effectiveness has not yet been proven, one reviewer stated that the authors needed to explain why the approach is therapeutic.

Several reviewers pointed out the need for clarification that just as psychiatric disciplines must consider biological and environmental causes before labeling an illness as psychiatric, so too, must biological disciplines examine psychiatric sources of illness. Considering one position to the exclusion of the other is not appropriate. These reviewers further stated that both psychiatric and biological mechanisms are involved in the etiology of most illnesses and both approaches need to be considered when diagnosing and treating patients.

PATIENT AND COMMUNITY ISSUES

Although these issues were not discussed at length by the reviewers, a few reviewers did emphasize the importance of examining the sociological, legal and economic impact of diseases such as CS upon the individual and community.

RECOMMENDATIONS

The reviewers differed in their assessment of the feasibility and implementation of the recommendations outlined by the authors. Some reviewers expressed the need for a better understanding of the numbers of people affected and consensus as to the definition of the illness before specific recommendations such as the establishment of a registry and the conduct of health studies can take place. Other reviewers recommended prioritizing the recommendations in recognition that sufficient resources may not be available within the State to conduct all the activities being recommended. One reviewer suggested that more research could be conducted on the national level that examines CS as related to indoor air issues, sick building syndrome, and the effect upon the immune system. Other reviewers expressed satisfaction in the recommendations with some stating that the recommendations should be considered as modest, a first step for the State, and that more needs to be done than was outlined in the recommendations by the authors.

12/19/89

APPENDIX C

RESPONSES OF THE AUTHORS TO THE EXTERNAL PEER REVIEW

The authors are grateful to the reviewers of the August report. We found the reviews to be constructively critical; they will provide helpful guidance in the preparation of a manuscript for future publication based on this report. Below we address four specific concerns raised in the reviews.

Objectivity of the Report

Some of the evidence for chemical sensitivity is anecdotal (and for the most part not double-blind) and much of this anecdotal evidence has been reported by clinical ecologists -- physician practitioners whose clinical practices have come under intense criticism. The authors, too, recognize the need for control populations, as well as double-blind challenges in the study of chemical sensitivity. We, however, are persuaded that the collective evidence, in part anecdotal and in part based on good scientific studies, does present a sufficiently compelling case to warrant future study.

It was beyond the scope of our original charge and consequently beyond the scope of our report to undertake a scientific critique of clinical ecology. Chemical sensitivity is by no means the exclusive property of clinical ecology. Occupational and environmental medicine contain sufficient examples to suggest a real medical problem. There has been an unfortunate amount of acrimony between allergists and clinical ecologists. This has lead to a hardening of positions on both sides. In our report we felt it would be counter-productive to add to these hostilities. We are certainly aware that there are some outlandish or questionable practices that have become identified with clinical ecology. However, our report focuses on the problem of chemical sensitivity and not on the practices of clinical ecology. We have attempted to draw on whatever sources are available to further our understanding of chemical sensitivity and to be objective in our evaluation of all the sources.

Definition of Chemical Sensitivity

Patients' reactions to environmental incitants can be assessed by either objective measures (e.g., FEV_1) or by the reporting of symptoms by patients. In either case, for research purposes and for validating the presence of sensitivity, these measures should be undertaken in double-blind, placebo-controlled fashion.

Our operational definition of multiple chemical sensitivity involves a two-step process:

(1) Removal of the patient from suspected incitants (de-adaptation) in an environmental unit, hopefully with clearing or diminution in symptoms;

(2) Recurrence of symptoms with re-challenge after an appropriate interval.

Causality is inferred when demonstrable relationships between specific symptoms and specific exposures are confirmed.

Acceptance of this definition for research purposes is necessary for scientific inquiry and ultimately validation of the existence of this syndrome. Such investigation, performed in a carefully constructed and operated environmental unit, is capable of elucidating cause and effect relationships between low-level chemical exposures and symptoms. Because critics may argue that merely placing a person in such a facility could have psychological effects, two important aspects of testing are essential for research in order to satisfy the most skeptical:

(1) Wherever possible, objective parameters, e.g., pulmonary function, brain waves, biochemical markers or other measures should be sought and measured before and after challenge to document changes;

(2) Double-blind placebo-controlled challenges should be conducted.

In cases where the only symptoms produced are subjective, e.g., nausea, headache, mental confusion or depression, then double-blind, placebo-controlled challenges should be performed with sufficient iterations as are theoretically necessary to yield statistically significant results. In some instances, subjective measures may be the most sensitive indications of subtle effects, e.g., central nervous system effects. There is an apparent dichotomy with regard to multiple chemical sensitivities concerning "objective" versus "subjective" measures with an all too frequent assumption that these two labels refer to symptoms that are "believable" and "unbelievable," respectively. In the special case (which we advocate for research purposes) where subjective reporting of symptoms of these patients is undertaken double-blind and placebo-controlled, "subjective" cannot be read as synonymous with "unbelievable." Using the design we propose, the patient acts as his own control. Once a unit is built and operating it would be important to address the responses of "normals," both physical and psychological responses, to the environmental unit in order to provide an additional baseline for comparison.

The operational definition is both sensitive and specific for research purposes. Clinical case definitions may prematurely close off investigation of groups of individuals because these definitions may be overly restrictive and may address only

a narrow sector of the affected population. Differences between groups studied in a unit may help elucidate important avenues for exploration.

Some reviewers thought we intended our operational definition to be used as a case definition for constructing a state-wide registry, i.e., patients would have to be worked up in an environmental unit prior to entering the registry. This was not our intention. In our view, a registry would include all physician-reported cases of chemical sensitivity and invite information to help identify which exposure(s) may have initiated the sensitivities, which exposure(s) subsequently trigger symptoms and what those symptoms are. From this universe of reported chemical sensitivities, more narrowly constructed groups could be targeted for investigation, e.g., if multiple complaints involving carpet installations or pesticide application were reported.

Clarification of the Use of the Environmental Unit

Some concerns were raised as to our heavy emphasis on the importance of the environmental unit in addressing the problem of chemical sensitivity. The unit is essential for documenting the existence of the problem for research purposes. In a minority of patients, the unit is necessary for diagnosis. For others, avoidance of exposures and testing on an outpatient basis may be sufficient.

Regarding the implementation of a unit, clearly careful selection and screening of patients who would enter a unit is needed. Polysymptomatic patients whose problems began after a clear-cut exposure to chemicals and who have failed outpatient work-up of their sensitivities would seem logical candidates. As experience is gained working with these patients, criteria for admission to the unit should be refined and perhaps broadened.

Upon entry, patients begin fasting which lasts at least 4 days and often longer. Intense "withdrawal" symptoms may appear in response to removal from incitants. Headache, malaise, joint aches, fatigue, depression and irritability are some of the more frequent symptoms patients report their first few days in a unit, after which they usually improve. Next they begin the rigors of food and chemical challenges. Patients whose conditions are very fragile, those who cannot undergo fasting, and those who cannot stop or taper off medications or give up smoking should not enter an environmental unit while in such condition.

Concerns were expressed regarding the ethics of exposing individuals to potentially hazardous substances, including possible carcinogens. Voluntarily or involuntarily, people expose themselves on a daily basis to levels of "toxins" much higher than those that would be needed for testing these patients. It must be borne in mind that X-rays are associated with an increased risk of cancer that must be balanced against their diagnostic value. Informed consent is imperative. Further, patients must have a clean environment to return home to and a social support network sufficient for their needs.

By performing individual, double-blind placebo-controlled challenges with objective measures before and after challenge, each patient serves as his or her own control. Since symptoms complexes and triggering substances vary widely from patient to patient, in our view the environmental unit is the preferable approach to studying chemical sensitivities.

Psychiatric Causes and Interventions

Two separate issues arise in the context of possible psychiatric origins or contributions to chemical sensitivity. The first relates to the plausibility, nature and extent of these contributions; the second concerns the most prudent approach towards diagnosis and treatment of the patient when both physiological and psychological factors might be involved.

Psychological symptoms are not necessarily psychological in origin. Advances in biological psychiatry focus on genetic and biochemical factors as contributors to central nervous system dysfunction and behavioral disturbance. Environmental exposures can also have psychological sequelae and we include references on this subject in our report.

One of the reviewers reminded us that there is evidence to suggest that psychosocial events, such as the death of a spouse or divorce, can suppress immune system function. This may predispose certain people to being more sensitive to chemicals at low levels. It is certainly worth emphasizing that the relationship between psychological and physiological systems is an intricate one.

Two of the most vocal critics of clinical ecology, allergists John Selner and Abba Terr, are of the opinion that multiple chemical sensitivity patients adhere to a "belief system" that chemicals are the cause of their health problems. Staundenmayer and Selner describe what they term "an irrational belief system":

> The ecology belief system usually is deeply entrenched and its logic well developed by intricate rationalizations and indoctrination. Social factors feed on the primary and secondary gain of the victim. "True believers" are more than willing to present their testimonials, seeking and affording mutual assurance. The social and psychological dynamics of the cult apply. In addition, there exists a plethora of "health publications" that provide the authority of print, while an impulsive media, eager for news, often is duped by unsubstantiated and unscientific claims of so-called ecology authorities.[1]

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[1]Staudenmayer, H., and Selner, J. C., "Post-traumatic Stress Syndrome (PTSS): Escape in the Environment," Journal of Clinical Psychology (1987) 43(1), 156-157.

Dr. Terr believes that no psychotherapeutic intervention will help these patients[2] while Dr. Selner advocates systematic deprogramming of the patients to purge them of their beliefs. Dr. Selner believes that 50-75% of receptive patients can be deprogrammed [Selner 1988, p 51]. Staudenmayer and Selner emphasize that it is necessary to separate those patients with chemical sensitivity who adhere to a belief system from those who are truly chemically sensitive.

Some psychologists and psychiatrists note an increased incidence of physical or sexual abuse, severe medical illness, loss of one or both parents or other major disruption in care-giving relationships during the childhood of "chemically sensitive" patients [Schottenfeld 1987]. These findings are based upon in-depth, personal interviews with affected individuals. According to Staudenmayer, at first many patients will not reveal these problems, but when trust is established in a therapeutic relationship, they will.[3] Whether persons with chemical sensitivities experience as youths more psychological trauma than the "average" was not determined. It would be important to know what percentage "normal" individuals undergoing the same degree of intensive psychological inquiry, would also confess to similar difficulties. Otherwise this particular aproach to the problem would have the same flaws the clinical ecologists have been accused of with regard to study design.

Even if it should be the case that chemically sensitive patients have had more early trauma, two other questions must be considered. First--could major psychological trauma somehow predispose individuals to developing bona fide sensitivities to chemicals? Ecology patients sometimes report a major life event as the onset of their difficulties; however, one must be aware that such life changes are frequently associated with changes in exposures, e.g., a move to a different home, a divorce or spouse's death or taking medications during stressful times. For example, consider chemical sensitivities that might arise during exposures from remodeling which could manifest as irritability or depression. If a divorce ensues, the development of chemical sensitivities might be attributed to the "stress" of the divorce; when in fact the sensitivities may have contributed to both the stress and the divorce. Staudenmayer and Selner[1] assert they have performed blinded chemical testing using sham challenges as controls with patients who claim to have this condition and that these challenges result in many false positives and false negatives. These [alleged] erroneous reactions by patients confirm the lack of true sensitivities and provide a point of departure for the psychologist to explore with patients their "belief system" about having chemical sensitivities. In examining the experimental design for these challenges, issues that must be addressed are:

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[2]Terr, A. (1989). Personal Communication, 19 December 1989.

[3]Staudenmayer, H., Presentation made at the Annual Meeting of the American College of Allergy and Immunology, 11 November 1989.

(1) Are subjects in a de-adapted state prior to the challenge so that extraneous exposures during and prior to the challenge (up to several days before) do not interfere with testing?

(2) Are open challenges performed first to confirm that the "placebo" (a "masking" odor, e.g., peppermint) is in fact a placebo and the "active" challenge is something to which the patient has had demonstrable reactions?

(3) What is the recency and latency of the patient's exposure to the substance being tested? In other words, has enough time elapsed (about a week or so) that the person is no longer adapted or reacting to his last exposure, but not so much time that the sensitivity has waned? Recency of exposure is recognized as a crucial variable in conducting challenges in patients with occupational asthma, for example.

Finally, with regard to the issue of childhood trauma or childhood illness, one must ask whether the parents and families of chemically sensitive patients (patients who often have psychological manifestations) might not also have such problems. According to ecologists, there does seem to be some genetic predisposition to this problem. Likewise, abusive or alcoholic parents of these patients may have suffered from unrecognized environmental sensitivities (see Health Effects section regarding alcoholism and drug abuse, neurobehavioral and psychiatric manifestations). Ecologists argue that major illness during childhood may have been the result of undiagnosed chemical sensitivities or that sensitivities may have been triggered by infection or medications that were administered, rather than viewing these events as a disruption in the care-giving relationship or the beginnings of secondary gain, i.e., seeking attention or nurturing via illness. Thus even if one could prove that childhood trauma or illness is more prevalent among patients, such a finding neither proves psychological interpretations or disproves chemical causes.

The issue of whether chemical sensitivity is a bona fide and potentially widespread problem or, rather, an "irrational belief system" held by fewer individuals who may be "systematically deprogrammed" is a critical one, one that merits thoughtful consideration and rigorous scientific inquiry.

The above discussion argues that chemical sensitivity may have physiological causes, psychological causes, or both. The search for a cause in a specific patient is most likely to lead a physician to pursue one avenue before investigating the other. Often it is only one avenue, however, that is pursued. There are two kinds of mistakes which the investigator or diagnostician could make: in pursuit of an environmental cause, true psychological causes could be ignored or, alternatively, in pursuit of a psychological cause, true environmental causes could be ignored. The consequences of making those mistakes are different. Pursuing the psychiatric route first may subject the patient to the complexities of establishing a therapeutic relationship and/or the prescribing of psychoactive drugs, and both may generate

doubts of the patient's mental health. In addition, psychotherapy may be unproductive if environmental causes are at work. Labelling a patient with a psychiatric illness may be pejorative when viewed from the perspective of an employer, co-workers, and family. It is no accident that psychiatric records are kept separate from the medical records of patients. In the event that psychoactive drugs are used, any hopes of unravelling an environmental cause or contribution to the patient's underlying condition may be greatly complicated. Alternatively, if one were first to pursue the investigation of environmental causes of the illness, especially with double-blind placebo-controlled study in an environmental unit, the patient may discover an environmental cause; even if he does not, the confidence or justification with which a psychiatric etiology would be pursued is strengthened. Workup in an environmental unit is unlikely to interfere with or complicate subsequent psychiatric workup and thus the making of a mistake in choosing this option (investigating environmental causes first) can be more easily remedied.

In summary, one can remain agnostic about which route is likely to uncover the truth regarding causation, but the costs of erring are significantly different regarding the two routes of investigation. We think that these facts are sufficiently compelling to justify the investigation of environmental causes first, before committing patients to potentially detrimental psychiatric interventions, such as long term psychodynamic psychotherapy or long term medication. Certain cognitive behavioral therapies, short term or focused, may be beneficial but should not be relied on to the exclusion of evaluating the chemical component.