特　集　「国際臨床環境医学会　旭川」

# The environmental aspects of chemical sensitivity

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## Introduction

The study of the effects of the environment upon the individual is now feasible due to new technology developed in the construction of environmental units[1-3]. Our observations reveal that individual or multiple organs may be involved. The brain is the target organ in only a subset of chemically sensitive patients and its involvement should not be confused with psychosomatic disease.

Over the last 20 years physicians and scientists at the Environmental Health Center in Dallas have had an opportunity to observe over 20,000 patients who had chemical sensitivity problems. These patients were studied under various degrees of environmental control. This experience is unique in the world and had resulted in numerous peer-reviewed scientific articles, chapters in books, and books on this subject. Studies have resulted in over 32,000 challenge tests by inhalation, oral or injection methods, of which 16,000 are double blind. Blood chemical levels and fat biopsies for organic hydrocarbons number over 2,000, while the measurement of immune parameters are over 5,000 tests. Objective brain function tests have been accomplished in over 5,000 patients. Other objective tests, like computerized balance studies, depollutant enzyme levels, and autonomic nervous system changes, as measured by the Iriscorder, number near 1,000.

We wish to share our finding with the participants of the Japanese Society of Clinical Ecology for the study of chemical sensitivity.

## DEFINITION AND PRINCIPLES

Chemical sensitivity is defined as an adverse reaction to ambient doses of toxic chemicals, at levels which are generally accepted as subtoxic, in our air, food, and water. Manifestation of adverse reactions depend on: 1) the tissue or organ involved; 2) the chemical and pharmacologic nature of the toxin; 3) the individual susceptibility of the exposed person (genetic makeup, nutritional state, and total load at the time of exposure); 4) the length of time of the exposure; 5) amount and variety of other body stressors (total load) and synergism at the time of reaction; 6) the derangement of metabolism that may occur from the initial insults.

To demonstrate cause-and-effect proof of environmental influences on an individual's health, one must understand several important principles and facts. These principles involve those of total body load (burden), adaptation (masking, acute toxicological tolerance), bipolarity, biochemical individuality, the spreading phenomenon, and the switch phenomenon. Each principal will be discussed separately.

## TOTAL BODY LOAD (BURDEN)

Total body load is the patient's total pollutant load of whatever source (usually from air, food, and water or surroundings)[1) 2) 4)]. The body must cope with this total burden;usually it must be utilized, expelled or compartmentalized. Total body load includes; 1) physical factors (e. g. hot, cold, weather changes, positive ions[5)], electromagnetic phenomena[6)], radon); 2) toxic chemicals (e. g. inorganics:Pb, Cd, Hg, Al, Br, etc., organics, pesticides, formaldehydes, phenols, car exhausts, etc.)[7-21)]; 3) biological (bacteria, virus, parasites, molds[22)], food[23) 24)]); 4) psychological or emotional factors also significantly affect the patient, confirmed by recent work in psychoneuroimmunology, linking the psyche and the neuroendocrine and immune systems[25-28)]. Failure to reduce the total body load prior to pollutant challenge will frequently yield inaccurate results. Accordingly, we believe it is essential to conduct investigative procedures in controlled environmental circumstances with the total load reduced.

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## ADAPTATION（MASKING, ACUTE TOXICOLOGICAL TOLERANCE）

Induced by the internal or external environment, adaptation is a change in the homeostasis（steady state） of body function with adjustment to a new "set point" [29-32] . Adaptation is an acute survival mechanism in which the individual "gets used to" a constant toxic exposure in order to survive, at the same time suffering a long-term decrease in efficient functioning and perhaps longevity. Selye was among the first to describe this compensatory mechanism[33] . Because of adaptation or tolerance, the patients, total body load may increase undetected because the perception of a cause-and-effect relationship is lost. With no apparent correlated symptoms, repeated exposures may continue to damage his immune and enzyme detoxification systems[34) 35] . The eventual result of continued toxic exposure over a period of days, weeks, months to years is end-organ failure[11] . Withdrawal or avoidance of an offending substance for at least four days will aid in reducing the total body load after which a controlled re-exposure challenge will reproduce cause-and-effect reactions. In these deadapted individuals, there is high reproducibility of these evoked reactions permitting the physician to acquire sound scientific information[36] .

## BIPOLARITY

After an exposure, the body initially develops a bipolar response of a stimulatory phase followed by a depressive phase[1) 29) 37] , usually with induction of immune and enzyme detoxification systems[38]. If the incitant is strong enough, or if substantial size or duration of exposure occurs, the induced enzyme and immune detoxification systems are depleted or depressed by overstimulation and overutilization. An individual may also initially experience a stimulatory reaction in the brain, perceiving the inciting substance not as being harmful, but as actually producing an energizing "high" . Therefore, he continues to acquire more exposures. After a period of time, however, be it minutes, months, or years, his body's defenses are adversely overstimulated and he develops disabling depression-exhaustion symptoms[31] . This stimulation and depression-exhaustion pattern has been observed with many pollutant exposures, including ozone[12) 30] . When studying the effects of pollutants upon adapted individuals, the stimulatory phase is often missed or misinterpreted as being normal, thus giving faulty data. Studies in the controlled environment, involving 16,000 challenges in 2,000 deadapted patients, has proven this bipolarity phenomenon repeatedly.

## BIOCHEMICAL INDIVIDUALITY

Biochemical individuality is our uniqueness, which largely accounts for individual susceptibility[39] . We have differing quantities and interactions of carbohydrates, fats, proteins, enzymes, vitamins, minerals, and immune parameters with which to respond to environmental factors. One simple example is the noted relationship between low serum magnesium levels and the HLA B35 genotype[40] . This biochemical individuality allows us to either clear the body of noxious substances, or to collect them and contribute to the body burden. Biochemical individuality is dependent on at least three factors:genetic endowment, the state of fetus's nutritional health and toxic body burden during pregnancy, and the individual's present toxic body burden and nutritional state at the time of exposure.

Some individuals, for example, are born with significantly lower quantities of specific enzymes（it may be 75%, 50% or even 25% of the normals） . Their response to environmental stimuli is often considerably weaker than those born with 100% of the normal detoxifying enzymes and immune parameters. Examples are the babies with phenylketonuria or the individuals with transferase deficiency, who do well until exposed to their environmental triggers, and then damage sets in. There are over 2,000 genetically-transmitted metabolic errors, suggesting that most of the population will have at least one abnormality[41] . Toxic volatile organic chemicals have been shown by Laseter to bioconcentrate in the fetus, increasing the acquired burden in some babies[42] . It is well known that some individuals acquire their toxic load at work or around their homes[42] . This changes with different seasons and weather conditions giving variable effects and responses over time. Extreme care must be taken in evaluation of each patient, who may exhibit unique clinical responses due to his specific biochemical individuality. As an example, it is well known that not all patients will exhibit every reported symptom associated with systemic lupus erythematosus（SLE） . Similarly, each patient exposed to the same environmental pollutant will react with his or her unique complex of symptoms. Because this vital fact is misunderstood, many studies are flawed when the wrong signs and symptoms are assessed for that individual.

## SPREADING PHENOMENA, SWITCH PHENOMENA POLLUTION FACTS

Spreading is a secondary response to pollutants that can involve new incitants or new target organs. Spreading that involves new incitants occurs when the body has developed increased sensitivity to increasing numbers of biological inhalants, toxic chemicals, and foods at increasingly smaller doses. At this time, overload becomes so taxing that a minute toxic exposure of any substance may be sufficient to trigger a response or autonomous triggering may occur. For example, a person initially may be damaged by a pesticide and then eventually have his disease process triggered by exposure to a myriad of toxic chemicals and foods, such as phenol, formaldehyde, perfume, beef, lettuce, etc[152].

Spreading may occur for many reasons. It may be due to a failure of the detoxification mechanisms' oxidation, reduction, degradation, and conjugation' brought about by pollutant overload, or it may occur because of depletion of the nutrient fuels of the enzyme or coenzyme, nutrient fuels, such as zinc, magnesium, all B vitamins, amino acid, or fatty acid. This depletion may account for the increasing inability of the body to detoxify and respond appropriately. The blood brain barrier or peripheral cellular membranes of the skin, lung, nasal mucosa, and gastrointestinal or genitourinary systems may be damaged, allowing previously excluded toxic and nontoxic substances to penetrate to areas that increase the risk of harm. Physiologic parameters including immune or pharmacologic releasing mechanisms, such as serotonin, kinin, and other vasoactive amines, may become so damaged that they are triggered by many toxic, then nontoxic (e. g., food) substances in addition to the specific one to which they initially reacted. It is well substantiated that antigen recognition sites may be disturbed or destroyed by pollutant overload. Hormone deregulation (feedback mechanisms) may occur, allowing for still greater dysfunction and sensitivity[152].

In contrast to patients who experience increased sensitivity to multiple triggering agents, some chemically sensitive patients may have one isolated organ involved in their disease process for years only to have dysfunction spread to other organs as their resistance mechanisms breakdown. This kind of spreading from one to another or multiple end-organs enables the progression of hypersensitivity and the eventual onset of fixed-named disease[152].

The switch phenomenon is the changing of pollutant-stimulated responses from one end-organ response to another. This change usually occurs acutely, but it may occur over a much longer period of time. This phenomenon was first described by Savage in the 1800s. He observed that when mental patients were at their worst they usually had a remission of their asthma or sinusitis. When they were better mentally and they were seen in the outpatient clinic, they had a much higher incidence of sinus and asthma problems. Randolph and most other environmentally oriented physicians have also observed this phenomenon. At the EHC－Dallas, we have observed similar occurrences in our patients, and, in fact, take cognizance of this phenomenon when evaluating therapy outcome[152].

In observing thousands of controlled challenges in the environmental unit, we have seen the target organ responses of many of our patients switch to several different ones during a long (i. e., 24h) reaction. Often, we have seen, for example, transient brain dysfunction followed by arthralgia, followed by diarrhea, followed by arrhythmia[152].

The switch phenomenon has also been seen following unsuspected or unrecognized pollutant exposures. For example, an individual sprays his home with pesticides and subsequently visits a neurologist with complaints of headaches and a rheumatologist with symptoms of arthritis. Never noticing or suspecting a connection between his exposure and the onset of his symptoms, he fails to disclose to either doctor symptoms unrelated to their specialty or the fact of his exposure. Instead, he submits to symptomatic treatment by both physicians. His health may temporarily improve, but in all likelihood, his total body load will remain elevated and he will become increasingly vulnerable to additional exposures that result in a still greater variety of symptoms[152].

Even when therapy for pollutant injury appears to have been effective, the switch phenomenon may be disguising the fact that the body is still harboring a pollutant. In this case, a new set of symptoms may begin indicating that a pollutant response has simply switched to another end-organ. This phenomenon occurs frequently when symptom-suppressing medication therapy or inadequate environmental manipulation is used over a period of time. For example, a patient may have his sinusitis cleared by medication (e. g., cortisone), but later since the cause has not been eliminated, he may develop arthralgia and eventually arthritis, or his colitis may have cleared only later to have cystitis develop. Because the occurrence of switch phenomenon is both common and insidious, it is essential that physicians monitor their patients for the onset

of any new symptoms or problems[152].

The switch phenomenon with its cluster of disparate symptoms signals a problem that is a part of a larger pattern needing further investigation. If physicians were cognizant of this phenomenon during initial patient evaluation, they could help curtail a lifelong progression of illness through better diagnosis and treatment[152].

In order to accomplish concise studies of the chemical sensitivity phenomena, one must understand some facts about environmental pollutants.

Modern technology's rapidly accelerating rate of growth has produced a wide variety of chemical products, that contribute to the total chemical environment. Recent studies show that nearly 50% of the global atmospheric pollutants are generated by man, (either isolated from natural products or synthesized), and the ubiquitous nature of the toxic chemical agents is widely appreciated[8) 13) 14)]. It has been estimated that more than 2,000 new chemical compounds are introduced annually, and that over 60,000 different organic chemicals are used commercially today.

The widespread presence of hazardous chemicals has rendered critical the environmental sensitivity problems described by Randolph[43] almost 40 years ago. While celebrated instances of gross contamination have long been the object of professional attention, only recently have literally thousands of synthetic chemical products, heretofore believed innocuous, have been incriminated ad agents of homeostatic dysfunction[11) 14)]. Current data affirm the view that standard methods for the determination of chemical incitants may no longer be effective[1) 7) 8) 26)]. With the finding that sensitivities can occur from subthreshold and picomolar quantities of chemicals, has come the discovery that standard procedures such as skin prick or scratch tests often fail to demonstrate positive reactions which are otherwise verifiable.

Recent literature confirms the harmful effects of chemical incitants, like formaldehyde[44) 45)], phenol[45) 46)], some pesticides[7)], chlorine[47)], and petroleum alcohol[48)]. Commonly encountered chemicals like glycine[9) 49)], DDT, toluene and turpentine[50-52)], and drugs such as hydralazine have been found to induce advanced-staged disease process[53)].

A number of familiar metals have also been incriminated, among them nickel, cobalt, chromium[54)], aluminum[55)], mercury[56)], and platinum[57)]. Other common environmental chemical incitants include xylene[58)], various acrylates[59)], and acrylated prepolymers[60)], benzoyl peroxide, carbon tetrachloride[61)], sulfates[62)], and dithiocarbamaes[63)], and diisocyanates[64)].

## WATER POLLUTION

Water has an important role in delivering contaminant minerals, toxic organic and inorganic chemicals, particulate matter and radiation to the human organism. In developed nations, the incidence of many chronic diseases, particularly cardiovascular disease, is associated with water characteristics, like purity and mineral content[13)]. Hardness or the lack thereof is involved in heart disease, hypertension, and stroke[13)]. Among the theorized protective agents found in hard water are calcium, magnesium, vanadium, lithium, chromium and manganese[13)]. Certainly, once cardiovascular pathology is induced, waters with high sodium content may be harmful. Other adverse agents include the metals cadmium, lead, copper, and zinc, which tend to be found in higher concentrations in soft water. Nitrates in water (usually from fertilizer) pose immediate threats to children under three months of age due to production of methemoglobin[65)], and sulfur can also cause reactions in susceptible patients.

City water, much of it secondhand, often contains from 100 to 10,000 times as many synthetic compounds as natural spring water[66)]. This, coupled with the rapid growth in the use of synthetic chemicals, has focused concern on the chemical quality of drinking water[13)]. Although microbes are important, attention is now being drawn to the microchemical contaminants. Advances in analytic chemistry has been able to reveal chemical contaminants in the parts－per－billion or parts－per－trillion range. It is a serious mistake to assume that extensive contamination of drinking water with "low" levels of synthetic pollutants is "normal". These chemicals are widespread, and we should not be lulled into assuming these contaminants are innocuous. Examination of our ground water has revealed many hundreds of toxic chemicals in these ranges[67) 68)].

Many examples of water contamination having been exposed, including Times Beach, Missouri, with winter floods flushing dioxin-contaminated oil used 20 years ago, Niagra's Love Canal area, Waterbury, Connecticut and Middleboro, Kentucky[69)].

In many cases, deadly materials have been accumulating for years in dumps and landfills. In the United States, some 80,000 pits and toxic wastes lagoons hold chemicals ranging

from carbon tetrachloride to discarded mustard-gas bombs[68]. Slowly escaping from burial sites, these leftovers directly contaminate our ground water. Polluted ground water exists at 347 of the nations 418 worst chemical dumps, and probably is occurring in the rest[68]. Laseter[7] and others[70] have shown that a virtual organic chemistry laboratory exists in most drinking water.

In the early 1980s, California, New York, New Jersey, Arizona, Nova Scotia, and Pennsylvania condemned dozens of public water supply wells due to trichloroethylene or tetrachloroethylene pollution[71]. Leaking fuel tanks contaminated nine Kansas public water supplies in 1981[71]. Officials in New Mexico identified 25 cities where hydrocarbons and solvents contaminated the ground water[71]. Analysis of New Orleans drinking water alone revealed the presence of 13 halogenated hydrocarbons.

Sources of water pollution fall into three major categories: 1) municipal sewage; 2) agricultural wastes;and 3) industrial wastes. Approximately 55% of the water treated in municipal plants is from homes, while another 45% is from industry. Agricultural wastes include those from livestock and toxic chemicals (pesticides, herbicides, fertilizers), and farm runoff collects in rivers, lakes, and ground water. Industrial wastes, however, contain some of our more toxic substances. Over one-half of the total volume of industrial wastes come from paper mills, organic chemical manufacturing plants, petroleum companies, and steel manufacturing. The major pollutants are chemical by-products, oil, grease, radioactive waste and heat. Other sources of contamination are drinking water disinfectants and by-products[68]; it should be remembered that chlorine, interacting with organic material, produces toxic trihalomethanes and other organochlorines. Alternatives to treating water with chlorine include ozone, chloramines, ultraviolet irradiation, iodination, or home reverse osmosis and charcoal filtration[68].

Chloride, added at many sewage treatment plants, can also react with organic matter in the water to form chlorinated hydrocarbons, many of which are also known to cause cancer. Copper sulfate, aluminum sulfate and fluorine are other major contaminants which may add to the total body burden[68].

Over a thousand different toxic chemicals have been found in public water supplies including pesticides, herbicides, industrial solvents, and polychlorinated biphenyls, just to name a few.

Inorganic pollutants include arsenic, cadmium, chromium, copper, manganese, mercury, silver, and selenium[13]. The use of inorganic arsenic insecticides has lead to high arsenic levels in some water supplies [13]. Barium (greater than 1 mg/L) has toxic effects on the heart, blood vessels, and nerves[68], while cadmium at levels greater than .0lmg/L has adverse arterial effects. At levels greater than I mg/L or one ppm, the following metals found as water contaminants have produced severe chronic toxicity:antimony[72], beryllium[73], cobalt[73], gold[73], iodine[13], lithium[73], mercury[14], and vanadium[73]. In Minamata, Japan, between 1953 and 1960, various plastic companies dumped methylmercury chloride into the water, producing 50 to 85 ppm of 12 mercury in nearby fish. Four hundred and six people died after ingesting these mercury-contaminated fish and the adverse toxicological effects in developing children are continuing to be measured[75].

A recently completed study[76], found that skin absorption contributed from 29 to 91% of the total body dose of pollutants (from water), with an average of about 64%. This is even more important when one looks at the large number of volatile organic compounds found in our drinking and bath water.

Radiation occurs in some waters in the form of radon, a naturally occurring radionuclide that seeps from rock and may be concentrated in airtight homes, especially the basements. At this stage, more information is needed to fully assess its effects. It probably, however, can increase the total body load.

In 1965, a serious drinking-water problem was seen in 40 percent of patients hospitalized for a program of comprehensive environmental control[1,77,78]. Today it is up to 80%. We have found that patients susceptible to water contaminants virtually always exhibit multiple sensitivities, with advanced and severe environmental reactions, especially to airborne chemicals[1]. Interestingly, water sensitivity in children was found to increase on a circadian and seasonal basis[79]. Increased severity was seen during June and July or in September and October, when grass, pollen, and mold counts were also high[79]. Some ECU patients had difficulty with waters containing high levels of sodium, others with calcium, and still others with high bicarbonate waters. A few individuals tolerated distilled water, even though it may contain some hydrocarbon residuals. Hundreds of outpatients have shown symptoms in reaction to both chlorinated and non-chlorinated waters, including numerous spring, charcoal-filtered, and dis-

tilled waters. If these water-induced symptoms remain undiscovered, food and chemical testing, may be distorted. It is vital to test and find safe water before proceeding with other testing in these severely sensitive individuals.

## CHEMICAL CONTAMINATION IN FOODS

The contamination if our urban food supplies is the result of widespread use of food additives, preservatives, and dyes in growth, manufacturing and processing. Virtually all commercially grown and prepared foods have pesticides and herbicides in them[9) 79)].

The literature abounds with reports of chemical sensitivities[80) 81)] to many additives. Contaminant reactions complicate the study of food sensitivity, forcing one to define more clearly the nature of the incitant, not only as it is encountered in foods, but in the air and water as well. Bell[82)] has reported urticarial reactions and immunological changes to exposures to a number of food additives. Condemi[83)] and Bell both suggest that food dyes may trigger reactions in sensitive individuals;including conditions commonly thought to be psychogenic, or certain forms of hyperactivity[28) 84-89)]. Lindemayer[90)] has associated urticarial reactions with several additives such as hydroxybenzoic acid propylester, benzoic acid, sodium benzoate, Ponceau rouge, and indigo carmine. Monroe's data indicate a casual role played by tartrazine azo dyes and salicylates in the provocation of vascular alterations[36)]. Other additives, including sodium nitrite and sodium glutamate, have been found to trigger migraine phenomena in susceptible patients[91)].

Sulfur dioxide[16)] and sodium salicylate can provoke asthmatic reactions[92)] while aspirin-like food contaminants and dyes may trigger urticaria, angioedema, bronchoconstriction and purpura[93)]. An even wider variety of symptoms, including severe gastrointestinal disorders, has been associated with sensitivities to aniline, commonly found rapeseed oil[94)].

In our experience, natural toxic components of foods, such as alkaloids, phenols, lectins, etc. must also be accounted for when studying the secondary food sensitivity which occurs from pollutant overload in the chemically sensitive. Therefore, three factors must be considered when evaluating the total food load. These are man-made pollutant contamination, natural toxic effects of foods, and food sensitivity. Failure to consider all three in the chemically sensitive patient may color or negate otherwise a clearly defined case of chemical sensitivity.

## CHEMICAL INCITANTS IN THE HOME ENVIRONMENT

Indoor air pollution in the home environment has produced a multitude of sensitivities to chemicals[8) 95)]. Time and space limitations allow only a cursory review of the numerous commercial hygienic products which can be noxious for chemically susceptible individuals. Among these are a wide variety of cosmetics[96) 97)], particularly those containing glycerin, propylene glycol, or butylene glycol[98)], perfumes[99)], and hair products such as dyes[100) 101)], creams[102)], sprays[103)], and shampoo[104)]. Moreover, sensitivities have been demonstrated to occur in association with lip salve[105)], fingernail preparations[106)], soaps[107)], sanitary napkins[108)], mouthwash[109)], antiperspirants[110)], contact lenses[111)], contact lens solutions[112)], and suntan lotions[113)].

Reports are widespread of sensitivities to chemicals in textiles, including synthetic acrylic fibers[114)], polyester spin finishes[115)], the epoxy resins, and synthetic clothing[116)]. Products such as fabric spray starch may also be considered toxic for the chemically sensitive individual[117)], for whom even the metallic buttons on blue jeans may trigger reactions to nickel[118)]. Formaldehyde[44)] on synthetics or tetrachloroethylene from dry-cleaned clothing can also produce problems.

Household cleaning products, particularly those containing formaldehyde, phenols and chlorine are hazardous for many patients. Several laundry products and detergents may be identified as household incitants[119)], as well as a number of products used to clean and polish furniture[120)].

The very construction of many homes may prove dangerous for the chemically sensitive patient. Data suggests that chemicals contained in wood preservatives (e. g., pentachlorophenols) are environmental incitants capable of triggering a variety of symptoms[121-123)]. Others report problems with reactions to formaldehyde-containing press board, carpets, plywood and petrochemical contaminants[124)].

Current data confirm earlier findings regarding the hazards of pesticides[125)] such as 2,4,DNP and fungicides[126)]. Moreover, research increasingly suggests the possibility of sensitivities to apparently innocuous items such as rubber bands[127)] coins[128)], epoxy[129)], and countless paper products[130) 131)]. Pesticides,along with oil, gas or coal are major offenders for sensitive individuals.

Research shows house plants[132) 133)], and common insects[134)] can now be viewed as environmental incitants or causes of homeostatic dysfunction. In addition, sensitivities to cold and

heat[36], and to contaminants in household water supplies have been associated with symptoms ranging from urticaria to severe respiratory distress.

Natural gas heat and stoves, and routine insecticiding or termite proofing of homes can be prime offenders in chemical sensitivity. One must consider these potential sources of contaminants when developing studies on chemical sensitivity. In our experience, failure to evaluate building and home environments before challenge testing will often make challenge studies invalid for the diagnosis of chemical sensitivity.

## MECHANISMS

The mechanisms involved in chemical sensitivity are becoming clearer, one of which has pollutant injury occurring to the lungs or liver, with resultant free radical generation[135]. Disturbances then occurs at the cellular, subcellular and molecular levels, producing injury either immunologically, or non-immunologically through enzyme detoxification systems. Vascular or autonomic nervous system dysfunction will then occur with one or a myriad of end-organ responses.

## IMMUNOLOGICAL

Type Ⅰ hypersensitivity is usually mediated through the IgE mechanism on the vessel wall. Classic examples are angioedema urticaria, and anaphylaxis due to sensitivity to pollen, dust, mold, or food[136], or some chemicals such as toluene diisocyanate. Ten percent of the patients with immunological involvement with chemical sensitivity seen at the EHC－Dallas seem to fall within this category.

Type Ⅱ cytotoxic damages may occur with direct injury to the cell. A clinical example of this is seen in patients exposed to mercury[137]. A group in Minamata, Japan developed neurological disease from eating fish exposed to toxic methyl mercury chloride. Mercurial pesticides fall into this category. Twenty percent of the patients with immunological involvement seen at the EHC－Dallas seem to fall into this Type Ⅱ category.

Type Ⅲ shows immune complexes of complement and gamma globulin damaging the vessel wall. A clinical example of this is lupus vasculitis. Numerous chemicals, including procainamide and chlorothiazide, are known to trigger the autoantibody reaction of lupus－like reactions. Many other toxic chemicals can also trigger the autoimmune response[138]. Other chemical, such as vinyl chloride, will produce micro aneurysm of small digital arterioles, probably due to this mechanism[51) 139].

Type Ⅳ (cell－mediated) immunity occurs with triggering of the T－lymphocyte. Numerous Chemicals such as phenol, pesticides, organohalides, and some metals will also alter immune responses, triggering lymphokines, and producing the Type Ⅳ reactions[138]. Clinical examples are polyarteritis nodosa, hypersensitivity angitis, Henoch－Schonlein purpura, and Wegener's granulomatosis[1) 139]. A recent study done at the Environmental Health Center－Dallas on 104 proven chemically-sensitive individuals (70 vascular, 27 asthmatic, and 7 rheumatoid), comparing them with 60 normal controls, showed that those manifesting a chemical sensitivity through their vascular tree had suppression of the suppressor T－cells (greater than 4 S. D.)[47]. Clearly the larger portion of our patients with immunological involvement fall into the Type Ⅲ and Ⅳ categories.

## NONIMMUNE ENZYME DETOXIFICATION

Nonimmune triggering of the cell and vessel wall may occur. Complement may be triggered directly by molds, foods, or toxic chemicals[139], and mediators like kinins, prostaglandins, etc. may also be directly triggered. These reactions then cause vascular spasm, with resultant hypoxia and release of lysozymes, which further produces more spasm, hypoxia, etc. Eventually end organ failure will occur.

Triggering of the enzyme detoxification, mostly in the systems of liver and respiratory mucosa, plays an important role in clearing of pollutants. It occurs, however, to a lesser extent in all systems. Foreign compound biotransformations have considerable variability, depending on genetic factors, age, sex, nutrition, health status, and the size of the dose.

The metabolism of foreign compounds usually occurs in the microsomal fraction (smooth endoplasmic reticulum) of liver cells. A few biotransformations are non-microsomal (redox reactions involving alcohols, aldehydes and ketones). There are basically four biotransformation categories oxidation, reduction, degradation, and conjugation.

The first three biotransformation pathways for xenobiotics are the same pathway that the body uses to process food and nutrients. If these enzyme systems are overutilized by competing foreign pollutants, inadequate handling of food proteins can result, with the subsequent induction of food sensitivities. However, because these detoxification pathways are dependent on nutrient and mineral cofactors, these systems are inducible by appropriate oral or systemic supplementation. Such supplementation serves as an important factor in stabi-

lizing and treating patients with chemical sensitivity. The fourth category of biotransfor-mation, that of conjugation, is almost exclusively for handling foreign compounds. Conjugation appears to be uniquely utilized for the catabolism of foreign compounds, using amino acids and their derivatives with peptide bonds, and carbohydrates and their derivatives with glucide bonds. Simpler compounds like sulfate and acetate are also involved in conjugation with linkage of ester bonds. Activated conjugated compounds plus specific enzymes are often detoxified by coupling with coenzymes;examples:coenzyme A with acetate and other short-chain fatty acids. Adenosine or phosphoadenosine phosphate is detoxified with a methyl group from sulfate methionine, or the ethyl group from ethionine. Similarly, uridine and phosphate with glucose and glucuronic acids[140) 141)].

There are generally five major categories of foreign-compound conjugative processes[140)]. These are: 1） acetylation through coenzyme A, for detoxifying aromatic amines and sulfur amides; 2） peptide conjugation with glycine, glutamine and taurine and aromatic carboxylic acids to hippuric acid; 3） sulfonation with glutathione（containing cysteine）, and microsomal enzyme conjugation for multi-ring systems such as naphthalene, anthracene, and phenoanthracene, which eventually results in benign mercapturic acids or alternatively benign sulfate esters; 4） alkylations by methionine of amines, phenols, thiols, noradrenaline, histamine, serotonin, pyridine, pyrogallol, ethylmucaptin sulfites, selenites and tellurites; 5） glucuronation. Glucuronides detoxify pesticides, alcohols, phenols, enols, carboxylic acid, amino hydroxamines, carbamides, sulfonamide and thio[140) 141)]. All of these processes are dependent upon nutrient fuels to keep these processes running efficiently. Toxic chemicals disturb the supply of the nutrient fuels by 1） producing poor quality food, 2） reducing intake, 3） reducing normal absorption, 4） setting up competitive absorption in the gut with nutrients, 5） imbalancing intestinal flora, 6） disturbing transport mechanisms, 7） disturbing proper decomposition and metabolism, 8） causing renal leaks, and 9） directly damaging nutrients. If nutrient inadequacy occurs, normal metabolism is overloaded and disturbed, resulting in selective changes in the pools of nutrients such as vitamins, minerals, amino acids, enzymes, lipids, and carbohydrates. Once this occurs, there is a vicious cycle of dysmetabolism, often with production or worsening of chemical sensitivity. These detoxification and metabolic defects are often measurable and have been accomplished in over 2,000 chemically sensitive patients.

## DIAGNOSIS

The diagnosis of chemical sensitivity can now be made with a combination of the following history, physical examination, immune tests including IgE, IgG, complements, T & B lymphocyte subsets, blood levels of pesticides, organic compounds, heavy metals（intracellular）, and occasionally objective brain function tests. Antipollutant enzymes, such as superoxide dismutase, glutathione, peroxidase, and catalase have been found to be suppressed in the chemically sensitive. Vitamin deficiencies, mineral deficiencies, and excess amino acid deficiency and disturbed lipid carbohydrate metabolism has been observed.

Challenge tests are the cornerstone of confirmatory diagnosis. These may be accomplished through oral, inhaled, or intradermal challenges. Care should be taken to rule out inhalant problems with pollen, dust, and molds. Food sensitivity occurs in approximately 80% of the people with chemical sensitivity and must be evaluated. When diagnosing chemical sensitivity, one must investigate water contaminant sensitivities, as 90% of people with chemical sensitivity have water contaminant reactions[4)]. This can be checked by placing the patient on less chemically-contaminated, charcoal filtered, distilled, or glass-bottled spring water for four days, with subsequent rechallenge of the patient's regular drinking water. This procedure will often elicit a reaction to the water pollutants in the sensitive individual.

Patients frequently know where and when the onset of their problems occurred, e. g., sudden exposure to pesticides, working around printing machines, factory machines, etc. They usually develop increased odor perception to gasoline, perfumes, new paints, car exhausts, gas stoves, fabrics, clothing or carpeting stores, chlorine and Clorox, and cigarette smoke. Not only will they find these smells offensive, but may have marked reactions to them as well. Other symptoms can range from the almost universally-seen fatigue, to classic end-organ failures. Physical findings frequently are vascular in nature, with edema, petechiae, spontaneous bruising, purpura, or peripheral arterial spasm. Frequently there is flushing, adult-onset acne, and a yellowness of the skin without jaundice. Chronic, recurring nonspecific inflammation is usually a significant sign, e. g., colitis, cystitis, vasculitis, etc. Laboratory

findings are often nonspecific, e. g., sedimentation rates may increase or liver profile may be mildly off. Fifteen percent of environmentally sensitive patients have positive C-reactive proteins. Twenty-five percent show abnormal serum complement parameters. Fifty percent of the chemically sensitive patients have depressed T cells. Twenty-five percent have impaired blastogenesis, and twenty-five percent have impaired delayed hypersensitivity, as evidenced by cell-mediated immunity skin tests. Of the patients with T-cell abnormalities, the depletion of the suppressor cells is seen, by over four standard deviations from a control group of normals[141]. Ten percent of these patients have elevated IgE or IgG. Patients with recurring infections have impaired phagocytosis and killing capacity. Very accurate blood measurements are now available for the chlorinated pesticides as well. The following were found in over 200 chemically sensitive patients:

| Pesticide in blood | % Distribution in 200 Patients |
|---|---|
| DDT and DDE | 62.0% |
| Hexachlorobenzene | 57.5 |
| Heptachlor Epoxide | 54.0 |
| beta-BHC | 34.0 |
| Endosulfan I | 34.0 |
| Dieldrin | 24.0 |
| gamma-Chlordane | 20.0 |
| Heptachlor | 12.5 |
| gamma-BHC (Lindane) | 9.0 |
| Endrin | 5.5 |
| delta-BHC | 4.0 |
| alpha-BHE | 3.5 |
| Mirex | 2.0 |
| Endosulfan II | 1.5 |

Organophosphate levels are only positive within 48 hours after exposure, and are not much help. Lab tests for pentachlorophenols and organic solvents like hexane and pentane, are also now available, as are herbicide levels. General volatile organic hydrocarbons are found in a large portion of chemically sensitive patients. Their presence indicates either recent exposure, or a failure in the enzyme detoxification system. Those found in over 500 chemically sensitive patients include benzene, toluene, trimethylbenzene, xylene, styrenes, ethylbenzene, chloroform dichloromethane, 1,1,1,-trichloroethane, trichloroethylene, tetrachloroethylene, dichlorobenzenes. Metals including lead, mercury, cadmium. and aluminum are sometimes found in the intracellular contents of some chemically sensitive patients. These again are found in 10% fo the patients.

Fat biopsies have been preferred on many patients with over 100 different compounds studied. Often there is more in the fat than blood in some cases such as organochlorine insecticides and more in the blood such as seen with such substances as 2-methylpentane and 3-methylpentane.

Skin biopsies of bruising and petechiae reveal perivascular lymphocyte infiltrates around the vessel wall in chemically sensitive patients.

Challenge tests can be done by the sublingual or intradermal route. The efficiency of these tests is now well established as numerous studies, (several double-blind), have now been done[4) 24) 47) 142-145)]. These need to be done since 80% of the chemically sensitive are food sensitive. Blind intradermal challenge for chemicals can now be done with terpenes, petroleum derived ethanol, glycerine, formaldehyde, phenol, perfume, and newsprint, whereby production of symptoms will help establish the patient's chemical sensitivity.

Over 200,000 intradermal challenges of chemicals have been performed under environmentally-controlled conditions at the EHC-Dallas. These are clearly reliable, especially as they meet the positive criteria of sign and symptom reproduction, wheal growth and negative placebo response.

Inhalation challenge is another method for the diagnosis of chemical sensitivity, done under varying degrees of environmentally controlled conditions. For best results one uses an anodized aluminum and glass booth to do ambient dose challenge of any toxic chemical in a hospitalized, environmentally controlled setting. Some studies done in our center, under strictly controlled conditions in an environmental unit, showed significant findings (4 S. D.) of the chemical reactors over the controls when using less than .20 ppm formaldehyde, less than .0025 ppm phenol, less than .33 ppm chlorine, less than .50 ppm petroleum derived ethanol, less than .034 ppm of the pesticide, 2, 4, DNP, along with 3 placebos. These tests have been used in over 3,000 patients with over 99% accuracy. Similar studies can be done in the office setting, although controls are much more difficult and one finds many more placebo reactions. This is because environmentally-controlled conditions are generally much more difficult to

achieve and patients are often studied in the masked or adapted state, wherein symptoms may not be perceived. With the inhaled challenges, one can. measure and plot blood levels, immune parameters, metabolic changes as well as sign and symptom scores.

Vitamin and intracellular mineral levels are needed to completely evaluate the chemically-sensitive individual. In our Center, analysis of over 300 chemically sensitive patients showed the following vitamin deficiencies:64% with B6 deficiency, 30% with B2, 29% with B1,27% with folic acid, 24% with vitamin D, 19% with B3, 6% with vitamin C, 3% with vitamin B12. Out of 190 chemically sensitive patients with mineral deficiencies, 88% had chromium deficiency, 12% selenium, 8% zinc, 40% magnesium and 35% sulfur.

A recent advance in the investigation of chemically sensitive patients is with brain function imaging by means of a SPECT scan（single photon emission computer tomography）. This scanning technique gives a metabolic or "biochemical activity" picture of the intracranial structures using a tracer which has been tagged with radioactive technetium-99.

Many chemically sensitive patients report problems with memory, concentration, emotional swings with irritability and poor mental organizational skills. These symptoms may have physiological triggers but may be mistaken for psychiatric symptomatology. A pattern commonly seen in the chemically sensitive patient closely resembles that of a neurotoxic affect on brain activity, with a pattern of diffuse intracerebral defects. This is frequently associated with neurocognitive symptoms, chemical exposures and chemical sensitivity. Frequently temporal lobe asymmetry is also seen, along with a mismatch between the brain blood flow and the amount of biological or biochemical activity[153].

In a recently completed study comparing chemically sensitive patients, healthy volunteer controls and non chemically sensitive patients, over 90% of the chemically sensitive patients have an abnormal brain scan of a neurotoxic pattern. Twenty-five out of 25 controls have been normal, and none of the non chemically sensitive patients scanned have shown a neurotoxic pattern.

This SPECT scanning technology provides evidence that the chemically sensitive patients are frequently found to have an abnormal cerebral metabolism, exhibiting a diffuse focal defect pattern that has previously been associated mostly with neurotoxic injury. The diffuse defect pattern may explain, in part, the complex neurocognitive symptoms that are frequently reported by chemically sensitive patients.

## TREATMENT

The cornerstone of treatment for chemical sensitivity is avoidance[146]. This will decrease total body burden, allowing recovery of the overtaxed detoxification systems. Less chemically contaminated water（including spring, distilled, and charcoal filtered), may be used, but only in glass or steel containers. Water will leach a variety of contaminants from the walls of synthetic plastic containers. A rotary diet of less chemically contaminated food, should also be used to reduce load and keep the patient in the unmasked state. Remove as many household incitants as possible, including petroleum-derived heat, insecticides, synthetic carpets and mattresses, and formaldehyde-containing substances such as press board and plywood. Toxic exposures can be monitored by the general volatile organic hydrocarbon blood tests. Some job changes may be needed, while occasionally the most severely affected patients have to leave badly polluted areas. Techniques should be developed for follow-up and monitoring of these modalities.

Injection therapy for inhalants, foods, and some chemicals will also help this proble[24) 144) 145) 147-150]. Low-dose sublingual therapy in patients with allergic rhinitis was effective[151]. These treatments can be done daily, but usually every four to seven days. In our opinion, a properly balanced rotary diet is essential in treating the patient with food sensitivity, whether or not it may be induced by chemical overload. Vitamin and mineral supplementation is often necessary to replace the deficiencies that occur from the direct toxic damage, exhausted enzymatic detoxification pathways, and from the direct competition absorption. In rare cases, nutritional replacement with intravenous hyperalimentation is needed for severely debilitated patients. Techniques should be developed for monitoring and evaluating the outcome. Heat depuration physical therapy has been used at the Environmental Health Center—Dallas in over 1000 patients. Clearly this modality will mobilize toxics and allow them to be eliminated from the body.

## IN CONCLUSION

The philosophy and techniques of environmental medicine developed over the last 25 years offers a means to scientifically investigate and treat patients affected by pollutants. This approach gives the physician valuable, accurate information in the pursuit of optimum health for these environmentally-

sensitive patients.

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