Chemical Hypersensitivity and the Allergic Response
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The widespread chemical contamination of the earth’s air, food, and water with its effects on various biological systems has been described in nearly 5,000 scientific articles. At present, chemical sensitivity can be defined as an adverse reaction to ambient levels of toxic chemicals, which are generally accepted as being "subtoxic," in environmental air (home and public buildings), food, and water. The manifestation of adverse reactions depends on the tissues or organs involved, the chemical and pharmacologic nature of the substances involved, the individual susceptibility of the exposed person (nutritional state, genetic make-up, and toxic load at the time of exposure), the length of time, amount, and variety of other body stressors (total load), and the possible synergism among these at the time of reaction.

It is often difficult, and at times impossible, to distinguish between allergic and toxic responses, and chemical sensitivities may encompass both. Chemical allergies involve an IgE or IgG response, and are a small but significant part of the overall spectrum of chemical sensitivity. An example is the IgE-mediated toluene diisocyanate antigen-antibody reaction. Another type has been found in survivors of acute poisoning who develop chemical sensitivity, but is usually not IgE- or IgG-mediated. In two large incidences—the gassing of troops during World War I and the cyanide accident in Bhopal, India—exposed persons have developed chemical sensitivities. In contrast, the etiology of those who have become chemically sensitive following long-term subacute toxic exposures is often difficult to discern. A significant number of persons are involved, perhaps as much as 20% of the population. The chemically sensitive person may develop reactions quite suddenly or gradually over a period of years. The concentration of chemicals needed to trigger a response diminishes and reaction to a minimal amount of toxic chemical may be possible. This progression is probably related to an overload of the enzyme detoxification systems. Chemical sensitivity is usually manifested in one main organ with secondary effects in others, and symptoms are usually multiple. The end-organ responses are often in the smooth muscles of neuro-cardiovascular, gastrointestinal, urogenital, and respiratory systems, as well as the skin, but any organ may be involved.

Much of the controversy about chemical sensitivity stems from the clinician’s inability to recognize the occurrence of environmental overload with subsequent application of appropriate clinical diagnosis and treatment to the individual patient.

Pathophysiology

The total body load is the total of all incitants to which the body has to respond to maintain homeostasis. Pollutants may be biological (pollens, dusts, molds, viruses, bacterias), chemical (organic or inorganic), or physical (heat, cold, electromagnetic radiation, light, radon, and
positive and negative ions). To prevent disease, the body must manage this burden through use or elimination. If the load is excessive, symptoms may occur as a response to disturbance of the body’s immune and enzyme detoxification systems.1

Acute toxilogic tolerance (masking, adaptation) is a change in the homeostasis (steady rate) induced by the internal or external environment, with accommodation of body function adjusting to a new set point.2 This adaptation or masking is an acute survival mechanisms in which the person apparently adjusts to a constant acute toxic exposure to survive initially but then later pays the price with a long-term decrease in efficient functioning and, perhaps, longevity. Because of this phenomenon, the total body load may increase without the person knowing. Even though no correlated symptoms are apparent, repeated exposures continue to damage the immune and enzyme detoxification systems, and the eventual result is end-organ failure. Avoidance of the offending substance for four days may unmask associated symptoms. Initial withdrawal symptoms may even occur. However, subsequent re-exposure will produce an immediate and clearly definable reaction because cause and effect are easily distinguished.

When exposed to a toxic substance, the body initially develops a bipolar response, with a stimulatory phase followed by a depressive phase.3 Induction of the detoxification systems occurs. If the incitant is virulent, biochemically active, or of substantial volume or duration, the detoxification systems may be depleted (depressed) by overstimulation. At the same time, a person may perceive a stimulatory reaction in the brain and initially feel that the inciting substance is not harmful but actually pleasurable. Therefore, the person may continue to subject him or herself to more exposures; with time (minutes to years), however, the body’s defenses can break down and depression-exhaustion symptoms develop. This stimulation and the resultant response has been observed with many pollutant exposures, including ozone.

Biochemical individuality accounts for individual susceptibility. Each person has differing quantities of carbohydrates, fats, proteins, enzymes, vitamins, minerals, and immune parameters with which to respond to environmental factors. This individuality allows us to clear noxious substances or to contribute to our own body burden. Biochemical individuality depends on at least three factors: genetics, the state of the fetus’s nutritional health and toxic body burden during pregnancy, and the person’s toxic body burden in later life in relation to nutritional state at the time of exposure. For example, some persons are born with significantly less of a specific enzyme. Although that person may be able to respond to an environmental stimulant, this response is often considerably less than that of the person who was born with 100% of the expected detoxifying enzyme and immune parameters.

**Environmental Pollution**

Recent studies have shown that nearly half of the world’s pollutants are generated by man,4 accentuating the problem described by Randolph5 more that 30 years ago. Literally thousands of synthetic chemical products heretofore believed innocuous have been incriminated as agents of homeostatic dysfunction. With the findings that sensitivities occur in association with picomolar quantities of chemical agents has come the discovery that procedures such as skin prick or scratch tests often fail to demonstrate positive reactions that are clinically verifiable by other means.

Recent literature verifies previous findings regarding the harmful effects of certain chemical
incitants, such as formaldehyde, phenol, chlorine, and petroleum alcohol. Commonly encountered chemicals, such as glycine, chlorphenothane, toluene, and turpentine, have been associated with the triggering of a plethora of vascular alterations, and some familiar metals, among them nickel, cobalt, chromium, aluminum, and mercury, have been implicated. Other common environmental chemical incitants include xylene, benzoyl peroxide, carbon tetrachloride, sulfates, and isocyanates.

Water Pollution

Minerals, toxic organic and inorganic chemicals, particulate matter, and radiation play an important role as pathways for chemical contaminants entering the human organism. The incidence of many chronic diseases (coronary disease, hypertension, and stroke) is associated with various water characteristics, including purity, hardness, and softness. Protective agents found in hard water are calcium, magnesium, vanadium, lithium, chromium, and manganese.

Certainly, once cardiovascular pathology is induced, waters with high sodium content may be counterproductive. Suspected harmful agents include cadmium, lead, copper, and zinc, which tend to be found in higher concentrations in soft water. Nitrates (from fertilizer) in water pose immediate threats to children under three months of age because of the production of methemoglobin. Sulfur will be a problem to some people.

City water today contains from 100 to 10,000 times as many synthetic compounds as natural spring water. Examples of gross water contamination include Times Beach, Missouri, with dioxin-contaminated oil used 20 years ago, the Love Canal area of Niagara Falls, NY, Waterbury, CT, and Middleboro, KY. In the US, some 80,000 pits and lagoons that hold toxic wastes ranging from carbon tetrachloride to discarded mustard-gas bombs have been reported.


Fifty-five percent of the water treated in municipal plants is from homes, and the remainder from industry (an important source of contamination). Over half of the total volume of industrial wastes comes from paper, organic chemical manufacturing plants, petroleum companies, and steel manufacturing plants. The major pollutants are chemical byproducts, oil, grease, and radioactive waste. Agricultural wastes include livestock and toxic chemicals (pesticides, herbicides, fertilizers) that run off from the farm lands into rivers, lakes, and groundwater.

Inorganic compounds contributing to pollution include arsenic, cadmium, chromium, copper, manganese, mercury, silver, and selenium. Asbestos may be a significant factor because over 200,000 miles of asbestos cement pipes are in use in the US.

In 1965, a serious problem related to drinking water existed in approximately 40% of patients hospitalized for a diagnostic therapeutic program of comprehensive environmental control; today, this figure is 80%. Patients susceptible to water contaminants exhibit multiple sensitivities. Many patients seen in the ECU with their unique metabolic individuality are even found to be intolerant.
of specific spring waters. Some have difficulty with waters containing high levels of sodium, calcium, or bicarbonates. If the reactions to specific water contaminants are undiscovered, evaluation of other incitants, including food and chemical testing, may be inaccurate. It is, therefore, necessary to find safe water before proceeding with other testing in severely sensitive persons.

**Food Contaminants**

The study of food sensitivity is complicated by the use of food additives, preservatives, and dyes in the manufacturing and processing of commercially available food products. This is forcing us to define more clearly the nature of the incitants in foods and water. Bell has reported urticaria, hyperactivity, and immunologic changes after food-contaminant exposure in sensitive persons. Urticaria has been described with several additives such as p-hydroxybenzoic acid propylester, benzoic acid, sodium benzoate, and indigo carmine. A casual role in the provocation of vascular alterations is played by tartrazine azo dyes and salicylates. Sodium nitrite and sodium glutamate have been found to trigger migraine in susceptible patients. Sulfur dioxide and sodium salicylate can provoke asthmatic reactions, and aspirin additives and aspirin-like food contaminant dyes may trigger urticaria, angioedema, bronchoconstriction, and purpura. Severe gastrointestinal disorders have been associated with sensitivities to aniline, commonly found in rapeseed oil.

**Home Contamination**

Indoor air pollution has spawned a multitude of sensitivities to chemicals. Numerous hygienic products may be noxious to the chemically susceptible person, including a wide variety of cosmetics (particularly those containing glycerin or propylene glycol), perfumes and hair products, such as dyes, creams, sprays, soaps, shampoos, and contact solutions. Chemicals in textiles, including synthetic acrylic fibers, polyester spin finishes, the epoxy resins, and synthetic clothing, may act as environmental antigens and are widespread. Many household cleaning products, particularly those containing formaldehyde, phenols, and chlorine have been shown to be hazardous for many. Chemicals contained in wood preservatives (pentachlorophenols) are environmental incitants capable of triggering a variety of symptoms. Others report problems with formaldehyde-containing pressed board, carpets plywood, and petrochemical contaminants. Pesticides and fossil fuels (oil, gas, and coal) are the number one offenders in homes.

**Occupational Contamination**

Because many workers’ symptoms improved during evening hours and weekends, heretofore "safe" occupations must be re-evaluated for potential hazards. Automobile factory workers exposed to polyurethane foam have been shown to be at significant risk, particularly because this industry uses a sizable number of chemicals, such as chrome, rubber, nickel, and isocyanates in spray paints, capable of triggering sensitivities. Occupation-related respiratory diseases are common among grain elevator workers and farm workers, who can demonstrate symptoms ranging from rhinitis to asthma. Abnormal responses may also be seen in persons who work with pesticides, herbicides, and farm equipment, as well as in persons employed in carpentry (contact sensitivities to woods), painting (severe respiratory symptoms), bricklaying (chemicals such as cobalt), hair care (variety of hydrocarbons), baking, photography, and film processing.
The list of occupations in which exposures to potentially hazardous chemicals may occur seems endless. What is remarkable, however, is the extent to which seemingly safe occupations are fraught with risks; for example, a chemically triggered reaction may occur in a concert violinist because of contact with rosin. Over the past three years, some 60 reports have associated dermatitis with chemical sensitivity in the work environment, including the latex surgical gloves and hand scrub solutions used by surgeons. Against the backdrop of present research, it seems clear that a virtually infinite number of occupations contain dangers for the susceptible person. Data clearly reveals the necessity of environmental control for the evaluation and treatment of such occupational sensitivities.

**Mechanisms of Sensitivity**

Our understanding of the mechanisms involved in chemical sensitivity is becoming clearer. Pollutant injury of the lungs or liver leads to free radical generation and subsequent disturbances at the cellular, subcellular, and molecular levels. This reaction can be either immunologic or nonimmunologic through the enzyme detoxification systems. Then, vascular-autonomic nervous system dysfunction occurs with a myriad of end-organ responses.

**Immunologic**

Type I hypersensitivity is usually mediated through the IgE mechanism on the vessel wall. Classic examples are angioedema, urticaria, and anaphylaxis caused by sensitivity to pollen, dust, mold, food, or chemicals, such as toluene diisocyanate. Of the patients seen at the EHC-Dallas, 10% seem to fall within this category.

Type II cytotoxic damage may occur with direct injury to the cell. A clinical example is the patient exposed to mercury. Twenty percent of the patients seen at the Dallas ECU fall into this category.

Type III immune complexes of complement and gamma globulin may damage the vessel wall. A clinical example is lupus vasculitis. Numerous chemicals, including procainamide and chlorothiazide, are known to trigger the autoantibody reaction of lupus, and other chemicals have been shown to trigger the autoimmune response.

Type IV cell-mediated immunity occurs with triggering of T-lymphocyte. Numerous chemicals, such as phenol, pesticides, and organohalide, as well as some metals, will also alter immune responses, thus triggering lymphokines giving the type IV reactions. Clinical examples are polyarteritis nodosa, hypersensitivity angiitis, Henoch-Schonlein purpura, and possibly Wegener’s granulomatosis. A recent study done at the Dallas ECU on 104 proven chemically sensitive (70 vascular, 27 asthmatic, and 7 rheumatoid) persons comparing them with 60 normal controls showed that those manifesting a chemical sensitivity through their vascular tree had a standard deviation suppression of greater than four of the suppressor T-cell population. Clearly, the larger portion of our patients fall into the type III and type IV categories.
Nonimmune Enzyme Detoxification

Nonimmune triggering of the vessel wall may occur. Complement may be triggered directly through the alternate pathway by molds, foods, or toxic chemicals. Mediators such as kinins and prostaglandins may also be directly triggered. These reactions then cause vascular spasm with resultant hypoxic release of lysozyme, which further accelerates the cycle with more spasm and hypoxia. Eventually, end-organ failure will occur.

Triggering of the enzyme detoxification systems also may occur in any organ but more frequently in the liver and respiratory mucosa. Foreign compound biotransformations vary greatly depending on genetic and environmental factors such as age, sex, nutrition, health status, and the size of the dose. For example, phenol may be excreted by the following pathways: phenyglucuronide (50%), potassium phenylsulfate (40%), guinol (10%), and catechol (1%). The metabolism of foreign compounds usually occurs in the microsomal fraction (smooth-muscle reticulum) of liver cells. A few biotransformations are nonmicrosomal (redox reactions involving alcohols, aldehydes, and ketones). The four basic biotransformation categories are oxidation, reduction, degradation, and conjugation. Because the first three are the same for nutrients, food problems are important in clearing and treating chemical sensitivity. The fourth category appears unique for the catabolism of foreign compounds using amino acids and their derivatives with peptide bonds and carbohydrates and their derivatives with glycide for bonds. Simpler compounds like sulfate and acetate are occasionally involved in conjugation linkage of ester bonds. Activated conjugated compounds and specific enzymes are often coupled with coenzymes from which they can be transferred to the foreign compound.  

Diagnosis

The diagnosis of chemical sensitivity can now be made with a combination of history; physical examination; immune tests, including IgE, IgG, complements, and T and B lymphocytes with subsets; blood levels of pesticides, organic compounds, and heavy metals (intracellular); and, occasionally, brain function tests. 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 must be considered, because it occurs in approximately 80% of persons with chemical sensitivity. Water-contaminant sensitivities must also be determined because 90% of persons with chemical sensitivity have water-contaminant sensitivity. This can be checked by placing the patient on chemically less contaminated water (charcoal-filtered, distilled, or glass-bottled spring water) for four days, with rechallenge with the patient’s usual drinking water.

Patients often know the location and time of the onset of symptoms. They may report sensitivity to the odor of gasoline, perfumes, new paints, car exhausts, gas stoves, fabrics, clothing or carpeting stores, chlorine and clorox, or cigarette smoke. Other symptoms can range from fatigue to classic end-organ failures. Physical findings frequently are vascular in nature and include edema, petechiae, spontaneous bruising, purpura, and peripheral coldness and arterial spasm. Frequently, flushing, acne (adult), and a yellowness of the skin without jaundice occur. Chronic
recurring signs of any organ system with chronic nonspecific inflammation, such as vasomotor rhinitis, colitis, cystitis, and vasculitis, may occur. Laboratory findings are often not specific: sedimentation rates may increase or liver enzymes may be mildly elevated, positive C-reactive proteins and abnormal complement levels can be found, T-cell levels may also be depressed and blastogenesis impaired. Finally, a number of patients will be found to have abnormal delayed hypersensitivities as elicited by delayed skin tests. As mentioned before, patients with T-cell abnormalities may have a suppressor-cell population that is more than four standard deviations lower than normal controls. Blood levels of pesticides are now available. Table 1 lists our findings in more than 200 chemically sensitive patients. Table 2 lists the volatile organic chemicals found in 114 patients studied from 1983 to 1986.

### Table 1

Blood Levels of Pesticides Found in 200 Chemically Sensitive Patients

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Serum Levels</th>
<th>Distribution (%)</th>
<th>Length of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT and DDE</td>
<td>0.3 ppb to 300 ppm</td>
<td>62.0</td>
<td>Chronic</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
<td>²</td>
<td>57.5</td>
<td>²</td>
</tr>
<tr>
<td>Heptachlor epoxide</td>
<td>²</td>
<td>54.0</td>
<td>²</td>
</tr>
<tr>
<td>Beta-BHC</td>
<td>²</td>
<td>34.0</td>
<td>²</td>
</tr>
<tr>
<td>Endosulfan I</td>
<td>²</td>
<td>34.0</td>
<td>²</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>²</td>
<td>24.0</td>
<td>²</td>
</tr>
</tbody>
</table>

² indicates patients with abnormal delayed hypersensitivity abnormalities.
<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Serum Levels</th>
<th>Distribution (%)</th>
<th>Length of Exposure¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrachloroethylene</td>
<td>0.3 to 500 ppb</td>
<td>83.1</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

¹Time from exposure to testing, in days.
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Time (days)</th>
<th>Sensitivity</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>2</td>
<td>63.2</td>
<td>2</td>
</tr>
<tr>
<td>Xylene</td>
<td>2</td>
<td>59.7</td>
<td>2</td>
</tr>
<tr>
<td>1,1,1-Trichloroethane</td>
<td>2</td>
<td>50.5</td>
<td>2</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>2</td>
<td>49.7</td>
<td>2</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>2</td>
<td>39.2</td>
<td>2</td>
</tr>
<tr>
<td>Chloroform</td>
<td>2</td>
<td>36.9</td>
<td>2</td>
</tr>
<tr>
<td>Benzene</td>
<td>2</td>
<td>23.4</td>
<td>2</td>
</tr>
<tr>
<td>Styrene</td>
<td>2</td>
<td>22.0</td>
<td>2</td>
</tr>
<tr>
<td>Dichlorobenzene</td>
<td>2</td>
<td>10.5</td>
<td>2</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>2</td>
<td>8.6</td>
<td>2</td>
</tr>
<tr>
<td>Trimethylbenzene (1984-1985)</td>
<td>2</td>
<td>3.2</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Time from exposure to testing, in days.
Unfortunately, organophosphate levels are only positive within 24 hours after exposure. Blood levels for pentachlorophenol and organic solvents like hexane and pentane are now available, as are herbicide levels. General volatile organic hydrocarbons, such as benzene, toluene, and xylene, are found in a large portion of chemically sensitive patients. Their presence indicates either recent exposure or a breakdown in the enzyme detoxification system. Metals, including lead and mercury, have been found in 10% of the patients studied. Challenge tests can be done by the sublingual route. The efficacy of this and intradermal challenged foods have been well established by numerous double-blind studies. These need to be done because 80% of the chemically sensitive patients are also food sensitive. Blind intradermal challenge for chemicals can be done with terpenes, petroleum-derived ethanol, glycerine, formaldehyde, phenol, perfume, and newsprint. Production of symptoms establishes the chemical sensitivity. More than 200,000 intradermal challenges of chemicals done at the EHC-Dallas were considered positive when they met the criteria of reproduction of signs and symptoms, wheal growth, and negative placebo response.

Inhalation challenge is another modality for the diagnosis of chemical sensitivity. This can be done under environmentally controlled conditions of many degrees. For best results, a stainless steel glass booth is used for ambient dose challenge of any toxic chemical. More that 16,000 ambient dose double-blind inhaled challenges of toxic volatile organic chemicals have been done in our center with accurate and reproducible results. Similar studies can be done in the office; however, under these circumstances controls are more difficult and many more placebo reactions may occur because environmentally controlled conditions are much more difficult to obtain and patients are often studied in the masked state.

Vitamin and intracellular mineral levels are needed to evaluate completely the chemically sensitive person. In our center, analysis of more than 300 chemically sensitive patients from 1984 to 1985 has shown a number of vitamin deficiencies: B₆ (64%), B₂ (30%), B₁ (29%), folic acid (27%), vitamin C (25%), vitamin D (24%), vitamin B₃ (19%), and vitamin B₁₂ (3%). Furthermore, of 190 chemically sensitive patients with mineral deficiencies, 88% had chromium deficiencies, 35% sulfur deficiency, 12% selenium, and 8% zinc deficiency.

**Treatment**

The cornerstone of treatment for chemical sensitivity is avoidance. This will decrease total body burden, allowing recovery of the detoxification systems. Chemically less contaminated water may be used including spring, distilled, and charcoal-filtered water, but only in glass and steel containers. Chemically less contaminated food on a rotary diet should also be used to reduce load and keep the patient in the nonadaptive state. As many synthetic substances as possible should be removed from the home, including petroleum-derived heat, routine insecticides, synthetic carpets and mattresses, and formaldehyde-containing substances, such as pressed board and plywood. A change in work areas is often needed. This can be determined by the general volatile organic hydrocarbon blood tests. Sometimes job changes are necessary, and occasionally the most severely sensitive patients have to leave certain polluted geographic areas.

Injection therapy for inhalants, foods, and some chemicals such as terpenes, perfumes, and petroleum-derived ethanol may also help alleviate a chemically-induced hypersensitivity. These
can be done daily, but usually are given every four to seven days. A rotary diet is also essential in treating any food sensitivities. Vitamin and mineral supplementation is often necessary to replace any deficiencies occurring from direct toxic damage, an increased metabolism required for detoxification, or competition with direct absorption.

Summary

Chemical sensitivity—the adverse reaction to ambient levels of toxic chemicals generally accepted as being subtoxic in the air, food, and water—is now becoming a well-recognized phenomenon. Widespread toxic chemical pollution of our air, food, and water trigger immune and enzyme detoxification mechanisms. This may result in adverse effects on the neurovascular, endocrine, gastrointestinal, respiratory (including ear, nose, and throat), genitourinary, musculoskeletal, and dermal systems. Laboratory parameters, including total eosinophil count, IgE, T&B lymphocytes, total serum complements, pesticide and solvent, and general toxic volatile organic chemical blood levels, are available to aid in diagnosis and treatment. The most definitive means of diagnosis are challenge tests by inhalation, oral, and intradermal exposures.

Bibliography


