Hypothesis for Induction and Propagation of Chemical Sensitivity Based on Biopsy Studies

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The reactive airways dysfunction syndrome (RADS), the reactive upper airways dysfunction syndrome (RUDS), the sick building syndrome (SBS), and the multiple chemical sensitivity syndrome (MCS) are overlapping disorders in which there is an intolerance to environmental chemicals. The onset of these illnesses is often associated with an initial acute chemical exposure. To understand the pathophysiology of these conditions, a study of the nasal pathology of individuals experiencing these syndromes was undertaken. Preliminary data indicate that the nasal pathology of these disorders is characterized by defects in tight junctions between cells, desquamation of the respiratory epithelium, glandular hyperplasia, lymphocytic infiltrates, and peripheral nerve fiber proliferation. These findings suggest a model for a relationship between the chronic inflammation seen in these conditions and an individual's sensitivity to chemicals. A positive feedback loop is set up: the inflammatory response to low levels of chemical irritants is enhanced due to the observed changes in the epithelium, and the epithelial changes are propagated by the inflammatory response to the chemicals. This model, combined with the concept of neurogenic switching, has the potential to explain many aspects of RADS, RUDS, SBS, and MCS in a unified way. — Environ Health Perspect 105(Suppl 2):473–478 (1997)

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Introduction

That chemical exposures can produce inflammation and that sensory nerves are involved in this process have been recognized since the early 1900s. In 1910 Bruce demonstrated that the inflammatory response to chemical irritants can be abolished by ablation of sensory nerves (1). This response is widely known. The red eyes, nasal congestion, and sinus headaches that arise from being stuck in the fumes of rush-hour traffic, sitting in a smoky bar, or painting with organic solvent-based paints are examples of inflammation from exposures to chemical irritants. This reactivity to chemicals can be altered in some people, and it is recognized that some people have a heightened inflammatory response to chemical irritants. A role for neurogenic inflammation in chemical sensitivity has been reviewed (2). This altered reactivity to chemicals is best known in rhinitis and asthma, with airway inflammation being triggered by chemical irritants. Hence, understanding chemical sensitivity in the airway may hold the key to understanding chemical sensitivity in general and the multiple chemical sensitivity syndrome.

My colleagues and I propose to study the nasal pathology of individuals with allergic and chemical irritant rhinitis, chemical sensitivity, and the multiple chemical sensitivity syndrome. Many of us believe, however, that chemical sensitivity is a major public health problem that is related to the epidemics of inflammatory conditions such as asthma and arthritis in industrialized countries. Understanding the asthma epidemic and understanding the multiple chemical sensitivity syndrome may be related, and the key to this process is understanding how an acute chemical exposure can produce ongoing inflammation in the airway and at other sites.

Reactive airways dysfunction syndrome (RADS) is a chronic asthmalike illness with onset related to an acute chemical exposure (3). Reactive upper airways dysfunction syndrome (RUDS) is chronic rhinitis with onset related to an acute chemical exposure (4,5). The distinction between these syndromes and the multiple chemical sensitivity syndrome (MCS) is that MCS patients have symptoms at sites other than the airway. This paper updates the progress of our nasal biopsy research program. Based on biopsy specimens of individuals with chemical sensitivity, a hypothetical model has been developed of the process by which an acute chemical exposure can lead to chronic inflammation. In essence, a single chemical exposure can induce a chronic disease. After a few general comments, preliminary biopsy findings and this model will be presented.

General Comments

Chemical sensitivity to inhalants refers to an abnormal sensitivity to a class of inhalants that is different from allergy to protein aeroallergens. Examples of this class of inhalants are given in Table 1. A number of case definitions have been given for

Table 1. Examples of inhalants associated with chemical sensitivity.

Products of combustion
Cigarette and cigar smoke
Furnace fumes
Gas cook stove and water heater fumes
Wood smoke
Gasoline-powered vehicle exhaust
Diesel-powered vehicle exhaust
Kerosene heater exhaust
Perfumes and fragrances
Perfumes
Detergents (grocery store soap aisle syndrome)
Products for cleaning
Pesticides
Petrochemical derivatives
Solvents
Glues and adhesives
Fresh paint
Fresh printing ink
Building material outgassing

chemical sensitivity syndromes (6), but what is constant throughout all descriptions is the inhalants involved. These inhalants are often complex mixtures that are ubiquitous in the environment of industrialized countries. Typically, these inhalants contain one or more odorous, low molecular weight, volatile organic chemicals. They are toxins, but the doses causing problems in chemically sensitive individuals are lower than the doses associated with classic toxicity.

In the early descriptions of chemical sensitivity, disease states associated with inflammation were prominent. Randolph described patients with arthritis, rhinitis, asthma, inflammatory bowel disease, and other inflammatory conditions that became

A

Respiratory epithelium

Basement membrane

Glands

Sensory nerve fibers

B

Respiratory epithelium:
tight junction defects
and desquamation

Basement membrane:
thickening

Glands: hyperplasia
lymphocytic infiltrates

Sensory nerve fibers:
proliferation

Figure 1. (A) Schematic of the elements of the normal respiratory epithelium showing the epithelial cell layer and the basement membrane. Glandular structures and sensory nerves are found in the subepithelial tissue. (B) Schematic of the deviations from normal seen in biopsy specimens of persons developing chemical sensitivity associated with rhinitis after a chemical exposure (9). There are defects in the tight junctions between respiratory epithelial cells, focal desquamation of the epithelial cells in places, hypertrophy of glandular structures, lymphocytic infiltrates, and proliferation of sensory nerve fibers.

asymptomatic when patients were fasted on spring water with control of both inhalants and ingestants in an environmental control unit (7). In addition, mental symptoms such as hallucinations, depression, and mania were described as improving when these patients were removed from the chemical environment. Elimination routines included both inhalants and ingestants. Symptoms were provoked by reexposure to foods and chemicals.

It is natural to consider neurogenic inflammation as a possible mechanism of chemical sensitivity. For many decades it has been known that sensory neurons are involved in an inflammatory process, and that this neurogenic inflammation is triggered by chemicals that stimulate these sensory neurons. For most people, these reactions are mild and fleeting and are resolved with the individual's removal to fresh air. For some people, exposures such as these can trigger debilitating illness with reactions lasting several days.

The work of Bascom and her collaborators is significant. A physiological response to inhalant chemicals was demonstrated in challenge studies with environmental tobacco smoke (ETS). As Bascom pointed out, this response is consistent with neurogenic inflammation (8).

My research in this area began when patients with chemical sensitivity were referred to an allergy clinic. These patients complained of an intolerance to chemicals associated with exposures to solvents or pesticides. Physical examination, particularly when supplemented with fiberoptic rhinolaryngoscopy, revealed severe inflammation of the upper airway in these patients. Findings included edema, abnormal mucus, cobblestoning (lymphoid hyperplasia), and friability of the mucosa. One puzzling finding that we consistently saw was focal areas of white mucosa with prominent blood vessels (4). Initially we thought this might represent atrophy of the mucosa, but biopsies performed for clinical diagnosis in selected patients revealed no atrophy, and no difference between the white and red areas of the mucosa. To our surprise, there was chronic inflammation of the mucosa with lymphocytic infiltrates in the biopsy specimens. A preliminary research study with controls was undertaken. The picture that is emerging is depicted schematically in Figure 1. Figure 1A is a schematic of the anatomy of normal respiratory epithelium.

Abnormalities of the nasal mucosa suggested by this study were lymphocytic infiltrates, glandular hyperplasia, proliferation of peripheral nerve fibers, gaps in the tight
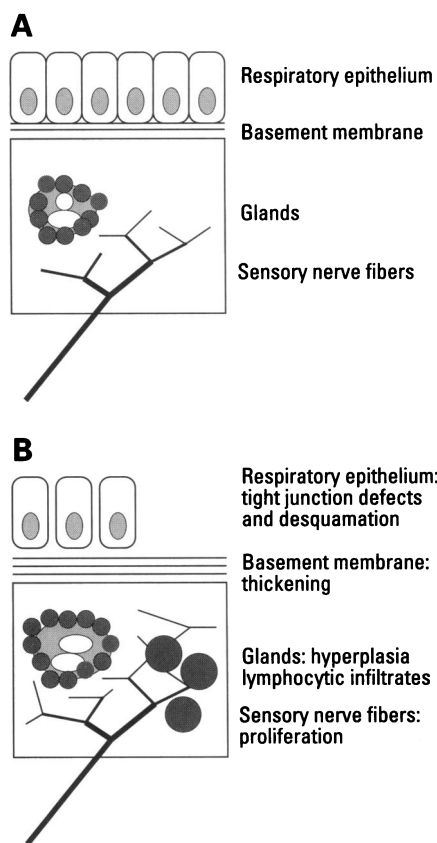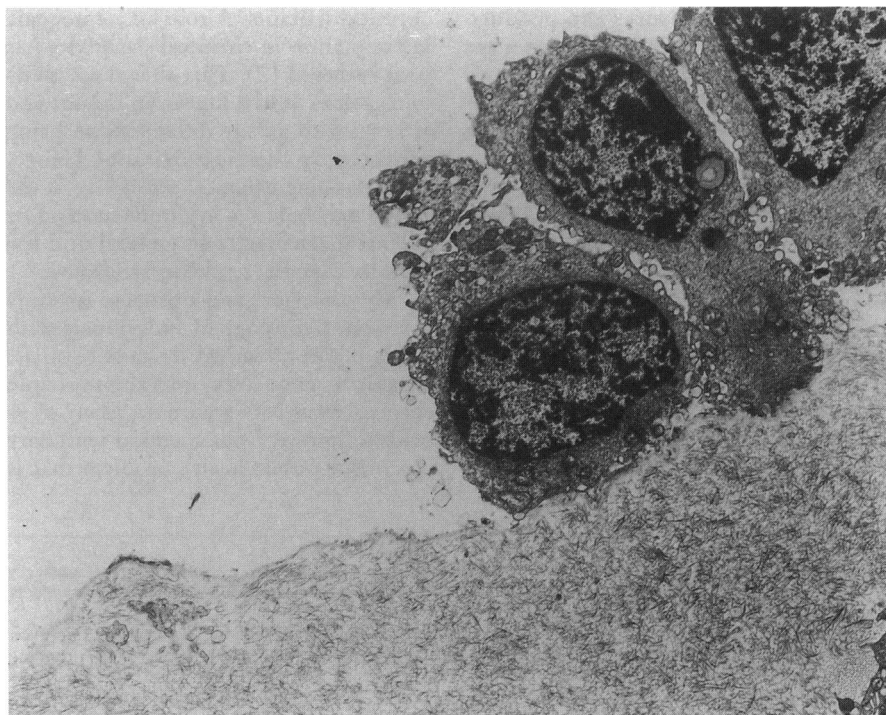
Figure 2. The nasal mucosa from a subject with chemical sensitivity associated with rhinitis is shown in an electron micrograph. Three epithelial cells are seen on the right with defects in the tight junctions between the cells. To the left, there is desquamation of the epithelial cell layer. The basement membrane appears to be thickened.

junctions between epithelial cells, and focal areas of desquamation of the epithelium (9). These abnormalities are depicted schematically in Figure 1B. An example of an electron micrograph of a patient is shown in Figure 2, with defects in tight junctions between respiratory epithelial cells and desquamation of epithelial cells visible. Attempts to study the distribution of substance P and vasoactive intestinal polypeptide (VIP) in these specimens with immunoperoxidase stains specific for these substances were unsuccessful because currently available reagents stain multiple sites in tissue specimens in a nonspecific pattern.

In the study by Meggs et al. (9), the presence of inflammation in patients relative to controls was statistically significant ($p < 0.05$). This study did not have the power to verify statistically the nerve fiber proliferation that was seen in chemically sensitive subjects relative to that in controls.

The challenge studies of Bascom et al. and Willes et al. (8,10) and these biopsy studies are complementary and supported by other evidence that airway inflammation is involved in chemical sensitivity. In a controlled study of patients with chemical sensitivity, Doty et al. (11) found significant increases in airway resistance in the chemically sensitive group. Welch (12) found significant exacerbations of preexisting allergic disease and new onset of asthma in patients with chemical sensitivity developing in association with carpet installation. Witorsch et al. (13) found that 100% of 61 patients meeting the Cullen criteria for the multiple chemical sensitivity syndrome had respiratory symptoms. Meggs and Cleveland (4) found that 100% of 10 consecutive patients referred to an allergy clinic with complaints of chemical sensitivity, all of whom met the Cullen criteria, had severe inflammation demonstrated by fiber optic rhinoscopy even if they denied upper respiratory symptoms.

It is easy to understand how chemical irritants trigger inflammation in the airway, and in fact the majority of patients with asthma and rhinitis report exacerbations related to these same irritants (14,15). In asthma, associations have been verified for perfume and tobacco smoke (14,16). Bascom et al. and Willies et al. verify an association between ETS and an inflammatory response in the upper airway (8,10).

Neurogenic Switching

How is it possible that stimulation of respiratory receptors by airborne chemicals can lead to involvement of other organ systems? It has been pointed out that this site switching is well known in allergic diseases (17). Food allergy can trigger urticaria, rhinitis, and asthma. Ingestion of foods or drugs as well as cutaneous inoculation with vespid venom can trigger systemic anaphylaxis. In experimental models of anaphylaxis, ablation of neuronal pathways eliminates the anaphylactic response without blocking histamine release or antibody production (18,19). This switching of the site of inflammation in allergy and chemical sensitivity may be due to the same mechanism: there are neuronal pathways from the site of stimulation through the central nervous system to other peripheral locations. This mechanism of site switching has been termed neurogenic switching (17). The pathways involved as well as the relationship between neurogenic inflammation and allergic inflammation are depicted in Figure 3. Table 2 characterizes allergic rhinitis, arising from mast cell degranulation in the upper airway as seen at Site B in Figure 3, and chemical irritant rhinitis, arising from substance P release from the sensory nerves, as shown at Site A in Figure 3.

Mechanism of Acquired Chemical Sensitivity

Biopsy findings suggest a mechanism by which an acute high-dose chemical exposure can lead to permanent airway inflammation and chemical sensitivity. The sensory nerve fibers that react to chemical
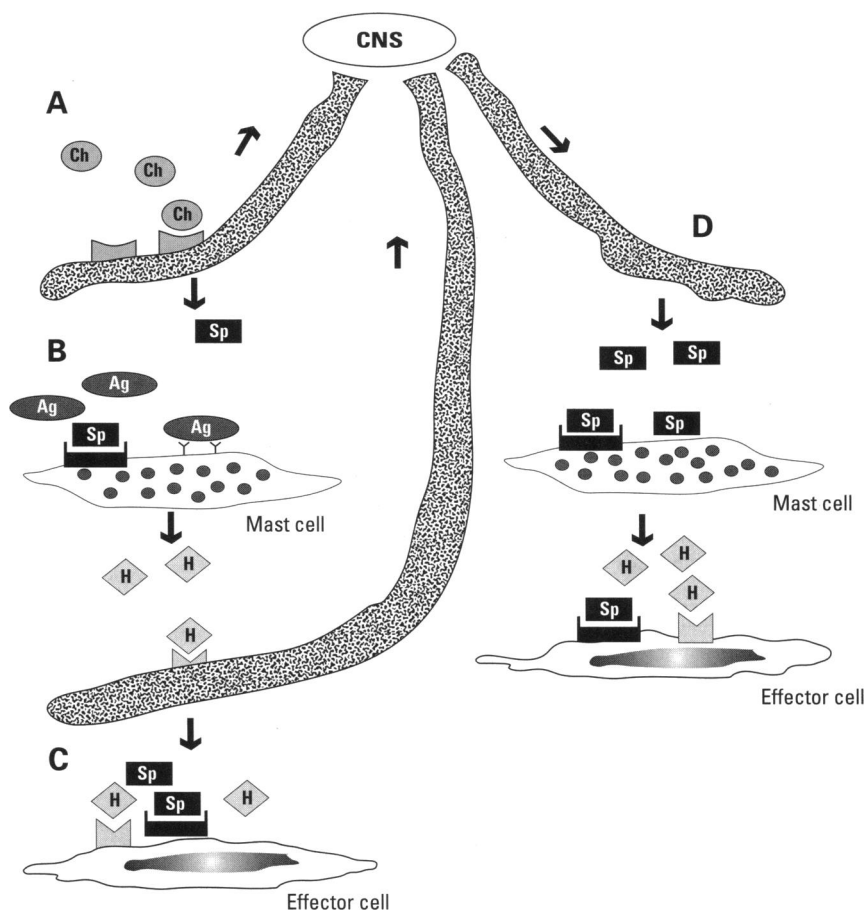

Figure 3. The relationship between allergic and immunogenic inflammation is depicted, with a proposed common mechanism for the site switching from the site of stimulation to a distal site of inflammation. At site A, chemical irritants, Ch, interact with sensory nerve fibers to trigger release of substance P, Sp, and other mediators of neurogenic inflammation. At site B, antigens, Ag, are depicted interacting with antibody on mast cells to release histamine, H, and other mediators of allergic inflammation. Histamine interacts with nerve fibers to produce signal transmission to the central nervous system. Site C depicts these mediators acting on effector cells to produce an inflammatory response. Site D depicts inflammation being triggered at a site distant from the stimuli. Signals from A or B are rerouted through the central nervous system to site D, where substance P, Sp, is released from the nerve endings to initiate an inflammatory response.

Table 2. Characterization of allergic rhinitis and chemical irritant rhinitis.

	Allergic rhinitis	Chemical irritant rhinitis
Trigger	Protein aeroallergens	Chemical inhalants
Target cell	Mast cell	Sensory nerve cell
Mediator released	Histamine	Substance P
Recruited cell	Eosinophil	Lymphocyte
Sensation	Itching	Burning
Symptoms	Rhinorrhea	Congestion
	Sneezing	Headache

irritants to produce inflammation are located beneath the epithelial cell layer, as seen in Figure 1. This cell layer acts as a barrier between chemicals in the airway and the nerve cells. It is reasonable to assume that a high-dose exposure can penetrate this barrier to trigger inflammation and can also damage this layer so that there is a loss of the epithelial layer. When the epithelial barrier is lost, neurogenic inflammation may be triggered at much lower doses. Hence, there is ongoing inflammation, which in turn continues the damage to the epithelial barrier. A proliferation of nerve fibers would mean that there are more receptors for chemical irritants and more inflammatory mediators to be released. The integrity of the tight junctions between epithelial cells is lost, and tumor necrosis factor is known to produce similar defects in tight junction integrity. One form of tumor necrosis factor is produced by lymphocytes, and lymphocytic infiltrates are seen in this patient population.

In summary, a positive feedback loop may come into play, with epithelial damage leading to a lower threshold at which chemicals produce inflammation. This inflammation in turn leads to ongoing loss of integrity of the epithelium. This feedback loop is depicted schematically in Figure 4. Another factor that may come into play is that lymphocytes may have specific antigen receptors for chemicals; this occurs in contact dermatitis. The details of the proposed mechanism are depicted schematically in Figure 5. Dotted lines indicate relationships that are at this time suggested by data but not rigorously established.

The proliferation of peripheral nerve fibers described here has been seen in other instances of inflammatory response and is termed remodeling (20). This remodeling effect may be produced by nerve growth factor activity, and it is known that lymphocytes have this activity (21).

Relationships between RADS, RUDS, and MCS

Three of the possible scenarios for the relationships between RADS, RUDS, and MCS are shown in Figure 6. If these disorders are separate, i.e., no relationships, one might see some incidental overlaps due to unfortunate individuals who may have two or all three of these disorders (Figure 6A).

Another scenario is depicted in Figure 6B, which suggests that RADS and RUDS are subsets of MCS. These patients would have MCS but have airway inflammation as a very prominent component of their disease. RADS is depicted as a subset of RUDS because patients with lower airway inflammation generally have some degree of upper airway inflammation. Figure 6C depicts the possibility that RUDS and MCS are the same disorder, with the primary lesion being upper airway inflammation and symptoms in other organ systems arising from neurogenic switching. Figure 6C is the scenario that is most consistent with my clinical experience. The patients I have seen with MCS, even those with predominantly mental symptoms and no complaints of rhinitis, have inflammation of the upper airway on physical examination. The patients I have seen with both RADS and RUDS all reported symptoms involving other organ systems related to chemical exposures, and all meet case definitions for MCS.

Pathogenesis of Inflammatory Conditions of Unknown Etiology

Does the mechanism proposed here play a role in conditions such as rheumatoid arthritis, inflammatory bowel disease, and migraine headache? Can chemicals in the airway enhance these disease states by switching the site of inflammation from the airway to other sites? Perhaps the pathophysiology of these conditions involves establishing neuronal pathways to the sites of recurrent inflammation. Multiple stimuli
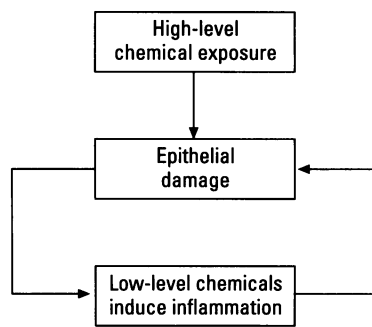
Figure 4. Proposed mechanism used to induce a high-dose chemical exposure to lead to sensitivity to low-level chemical exposures via epithelial damage. A positive feedback loop is created in which ongoing low-level exposures perpetuate epithelial damage, which in turn leads to a lower threshold at which chemicals will damage the epithelium.
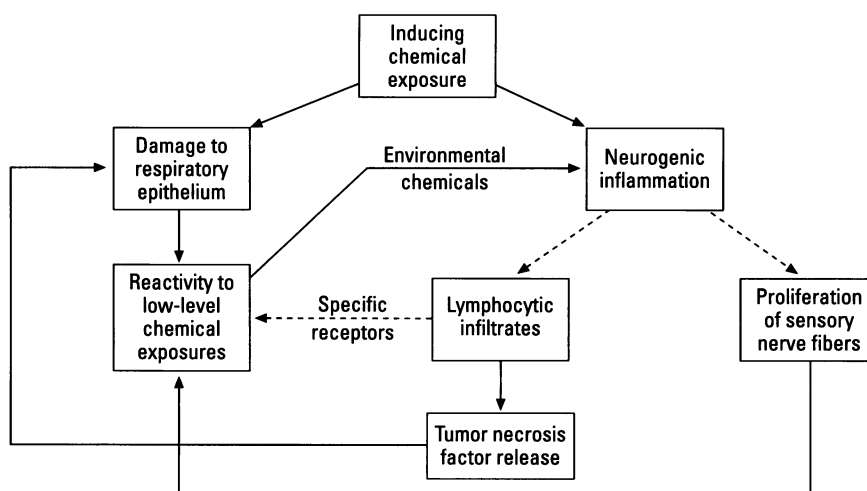
Figure 5. Details of the proposed mechanism for ongoing inflammation and chemical sensitivity following an inducing high-dose chemical exposure. Dotted arrows show relationships that are speculative and warrant further investigation.
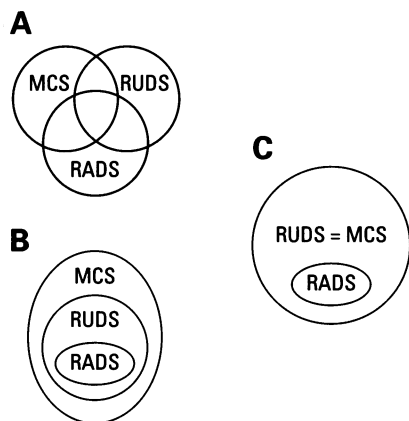
A

B

C

Figure 6. Venn diagrams depicting possible relationships between RADS, RUDS, and MCS.

such as chemicals in the airway, infections, allergies, and emotional stress could result in excitation of these pathways.

Research Needs

Much work is still to be done on this model, as summarized in Table 3. Basic science needs include the elucidation of the chemoreceptors on the sensory nerves. These receptors are thought to be proteins on the sensory nerve membranes and need to be isolated so they can be sequenced and have their structures studied. Clinically, there is a specificity to the response to chemicals. Some patients with severe chemical sensitivities have been known to tolerate substances that are devastating to others. For example, not all patients with asthma are aversely affected by exposure to

Table 3. Basic science and clinical research needs.

Basic science needs
Isolate chemoreceptors
Sequence chemoreceptors
Study structure of chemoreceptors
Study mechanism of chemical specificity— chemoreceptors vs lymphocytes
Study mechanism of nerve fiber proliferation
Determine role of tumor necrosis factor
Study the neurological pathways of neurogenic switching
Clinical science needs
Conduct further biopsy studies in RADS, RUDS, MCS, SBS
Expand control groups
Develop experimental models of the induction and propagation of chemical sensitivity
Conduct challenge studies
Conduct studies of inflammatory conditions in environmental control units
Study treatment of chemical sensitivity

cigarette smoke; however, it can be devastating to other patients. Is there a chemoreceptor specificity, or does the specificity lie with the lymphocytes? Chemical specific receptors on lymphocytes are known to occur in contact dermatitis, and a similar situation may exist in the airway. What is the mechanism of the peripheral nerve fiber proliferation suggested in patients' biopsies? Do lymphocytes or nerves produce a factor that causes this proliferation? What is the mechanism by which gap junction integrity breaks down? Is tumor necrosis factor involved in this process?

Clinical science needs include further biopsy studies in both humans and other species. Larger control groups are needed,

including normal subjects, patients with allergic rhinitis and allergic asthma, patients with asthma and rhinitis related to chemical exposures, and chemically sensitive patients without rhinitis. Biopsy studies should be combined with challenge studies to aid in assigning patients to groups. The problem of nonspecific staining of monoclonal antibodies to substance P, VIP, and neutral endopeptidase should be addressed, and functional assays may be necessary to establish the role of these substances in chemical sensitivity.

The role of chemical sensitivity in inflammatory conditions of unknown etiology such as inflammatory bowel disease, rheumatoid arthritis, and other collagen vascular diseases should be elucidated. This work can only be done in environmental control units because adapatative phenomena and masking are so prominent in these populations under study.

Most importantly, clinical research must be done to improve treatment of chemically sensitive patients. Do anti-inflammatory medications such as nonsteroidal anti-inflammatory drugs and topical steroids have roles in the treatment of chemical sensitivity patients? Do the substance P inhibitors now in clinical trial have roles in the management of chemical sensitivity? Does avoidance of chemical inhalants reduce reactivity to chemical irritants? Does the nasal epithelium heal if the patient is removed from the chemical environment? Does this healing result in the patient having decreased reactivity to chemicals?

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