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ENVIRONMENTAL ILLNESS: A DISORDER OF IMMUNE REGULATION

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INTRODUCTION:

The massive increase in our environmental exposure to chemicals, both synthetic and natural has altered our bodily makeup. It is now all but impossible to find an American that does not have a detectable level of synthetic chemicals like halogenated hydrocarbons in their body (34). The environmental concentrations of natural chemicals such as ammonia and formaldehyde are many orders of magnitude higher than in the past. Humans have many biochemical scavenger systems which protect them from damage caused by chemically altered cells and proteins. However, since we are now exposed to much higher concentrations of natural chemicals as well as massive amounts of synthetic chemicals to which our ancestors were never exposed, it is easy to see that in regards to chemical exposures, our protective resources are taxed to a much greater extent than was theirs.

Intense exposure to high levels of toxic chemicals often causes cell death. The clinical symptomatology associated with this type of damage has long been recognized as the acute toxic effects of chemical exposure and has been well documented in the medical literature (4,11,22,24,43). Lately, physicians have become aware of the effects of chronic low level exposure to toxic chemicals and their effect on the biologic regulatory mechanisms of the body. These factors serve as a foundation for the recognition of the disease called environmental illness.

In this chapter we would like to address the following issues:

1. What is the definition of enviornmental illness?

2. What is presently known about the pathophysiology of the illness?

3. How is the diagnosis made?

4. Etiological considerations in environmental illness?

5. How is environmental illness treated?

6. How can it be prevented?

I. DEFINITION

The term enviornmental illness is used to describe an acquired disease characterized by a series of symptoms caused and/or exacerbated by exposure to environmental agents. The triggering agents include industrial and domestic chemicals, cigarette smoke, diesel fumes, and alcoholic beverages. The symptoms involve multiple organs in the neurologic, endocrine, genitourinary and immunologic systems. There is a large body of information documenting symptoms seen in individuals subjected to known acute or chronic exposure to given chemicals; the only truly novel aspect of environmental illness is the realization that similar symptom complexes frequently are seen in individuals without known "massive" exposure and the diagnosis can be made on the basis of these symptom complexes.

II. SIGNS, SYMPTOMS, AND LABORATORY FINDINGS

The more common symptoms are outlined as follows:

A. Neurologic:

Patients report headaches, often migrane in nature.

Mental status changes mimicing a mild variant of Wernicke's encephalopathy are common. Patients describe a loss of short term memory which is characterized by the need to carry paper for lists and notes, and inability to find their way to new destinations. They commonly describe going to a store and forgetting what they came to buy. They also describe dulling of cognition with smog and deisel fumes such that they commonly miss familiar freeway exits while driving. People may also describe hearing their name called from a distant part of a quiet house when they are alone at home. Blood tests fail to show thiamine deficiency in these patients. Careful neuropsychological testing can identify various characteristics of this encephalopathy (7) which have previously been associated with exposure to certain chemicals (15,56).

Visual anomalies mimicing migrane aura are common complaints. Patients see fleeting visions in the periphery of the visual fields.

Peripheral neuropathies presenting as impairment or loss of peripheral sensation are often encountered. These can be documented on physical examination by loss of sharp/dull descrimination in the extremities and electromyographic

(EMG) abnormalities. People whose jobs require fine motor control describe themselves as "clumsy". An increase in the number of falling accidents is seen in this population (46). Acute loss of bowel or bladder control as a result of environmental exposure is another common complaint. Magnetic resonance imaging scans of the brain in such patients often show areas of increased signal intensity consistant with demyelination or micro infarcts.

Cardiac conduction system anomalies are commonly seen in this population. 24 hour Holter monitering demonstrates episodes of dysrhythmias when the patient is exposed to the triggering agent (20,25,38,39,42,44).

Acquired alcohol intolerance is another common complaint. Patients who were previously able to tolerate alcoholic beverages commonly describe getting sick or drunk very quickly, often with a single mouthful of an alcoholic beverage.

B. Endocrine:

Amennorrhea or dysmennorhea is commonly found in females. Testing may demonstrate primary hypothalamic failure in these patients.

Fatigue and cold intolerance mimicing thyroiditis is another common complaint. Many such patients can be found to have anti-thyroid microsomal or thyroglobulin antibodies which often predate development of frank abnormalities in thyroid

function tests. Occult thyroiditis is far more prevalent than prevously thought (14).

Fatigue, depression, and carbohydrate intolerance mimicing mild adrenal insufficiency is another common complaint. Cortrisin stimulation tests not infrequently reveal minimal adrenal reserves in these patients.

C. Genitourinary:

In addition to dysmennorhea, there is a high incidence of miscarriages, congenital anomalies, and genitourinary tract disease requiring hysterectomy (26). The incidence of cancer of the female reproductive tract is markedly increased in some populations (26).

D. Immunologic:

Chemically induced immune dysregulation is a recognized medical disorder (22). A wide variety of symptoms referable to immune dysregulation can be seen in this population. Skin manifestations such as urticaria and induration are common. When exposure to toxic chemicals is through the GI tract, such as contaminated drinking water, perianal pruritis may be found.

Arthralgia with swelling but without morning stiffness is a common complaint in this population. Rheumatoid factor is usually not detected on blood tests.

Chronic nausea with acquired food intolerance is a frequent complaint. This is a well recognized finding in chronic

toxic chemical poisoning (7,13). Food intolerance symptoms include all of the above mentioned nervous system symptoms, skin rashes, diarrhea, and bloating. Intradermal skin tests often confirm an immediate (IgE or IgG4) or a 24 hour delayed (IgG1 or 2) reaction to certain foods like milk, sugar, wheat, corn, and refined carbohydrates. Serial assessments of blood often show increased immune complexes associated with lowered complement components in response to ingestion of the suspect foods (6,37).

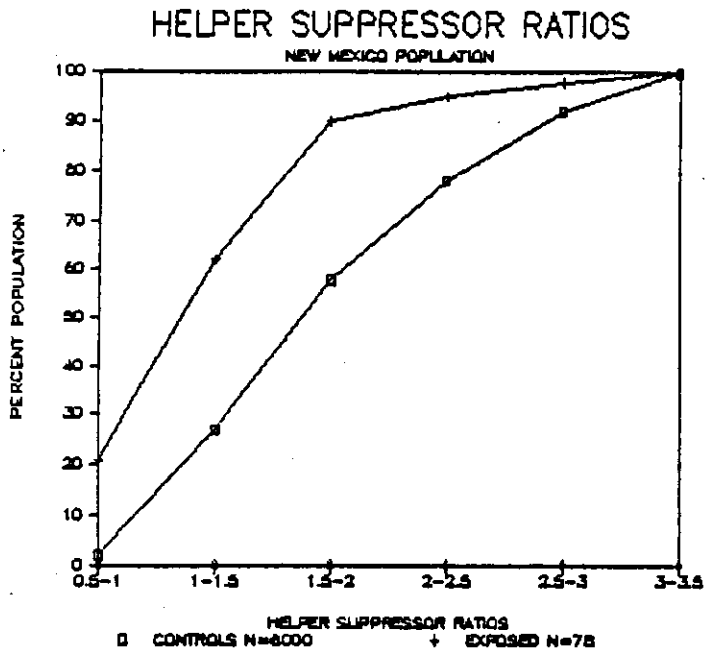
Other symptoms referable to immune dysregulation include an increase in intensity of ordinary type 1 (IgE, IgG4 mediated) allergies and increasing sensitivity to body molds such as candida albicans and trichophytin. Mold allergy can manifest itself clinically as chronic dermatitis, gastroenteritis, and endogenous depression (10,53).

Many patients respond inappropriately to viruses. This is manifested by the presence of the Epstein Barr Early Antigens (restricted and diffuse) long after the acute mononucleosis illness, presence of Hepatitis B Core antibody in the absence of Hepatitis B surface antibody indicating ongoing viral replication, and a protracted presence of IgM antibodies to the Cytomegalovirus (12,33). These patients have been classified by some physicians as suffering from a "chronic viral syndrome" (5,18,49). A large portion of this population can be found to have IgG subclass deficiencies (35,48). Inital evidence of this state comes

from the recognition that the adult patient with documented evidence of recurrent infections has a total IgG which is below the median for the expected range (1050 mg/dl). Subsequent measurement of IgG subclasses reveals a defeciency of one or more subclasses in majority of these patients. Recent evidence suggests that some of this population suffers from infection with the Human B Lymphocytotrophic virus (HBLV) (19,41,55).

Slight leukopenia is another common finding in these patients. Patients rarely have total white cell counts above 5500/cu.mm. Assessment of lymphocyte subpopulations often demonstrates low B cells and commonly shows low total T cells. Helper suppressor ratios are abnormal in a statistically significant number of these patients. These can be abnormally high or low, although the latter condition is more common. This is a reflection of an inordinately high number of suppressor cells rather than a diminution of helpers. This has led one investigator to postulate that these cells may be a population of natural killer cells which carry the CD 8 antigen (OKT 8,LEU 2)and is responding to a chemically transformed somatic cell (9). Assessment of the data presented in a recent report appears to demonstrate these same findings although the author concludes differently (52).

A study of 78 females exposed to over 600 different chemicals in a computer manufacturing plant demonstrated



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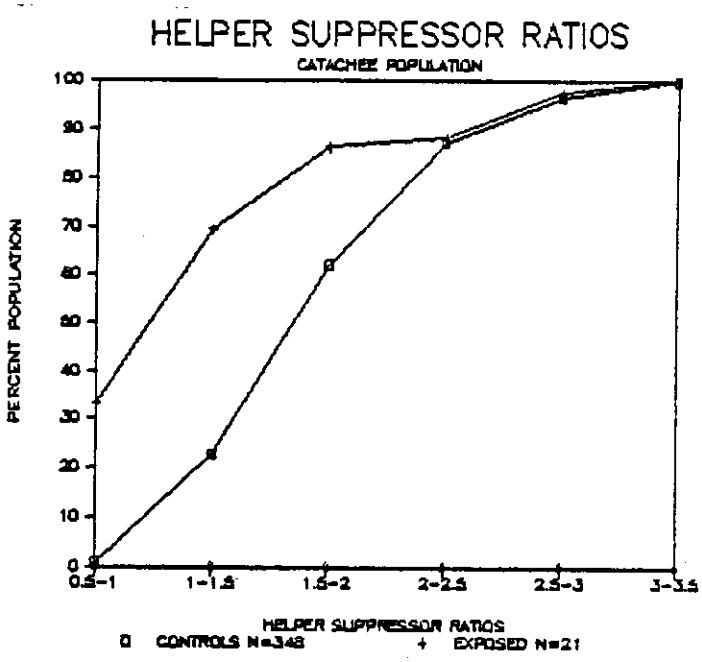

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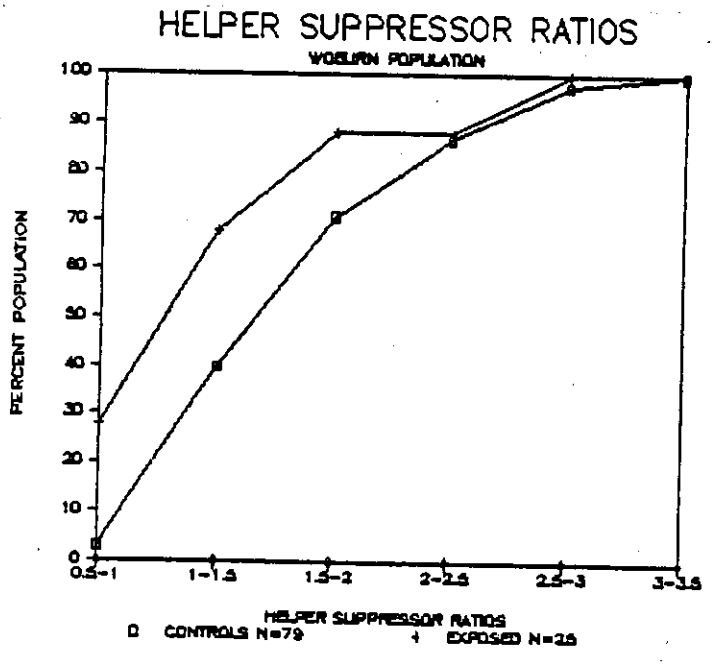

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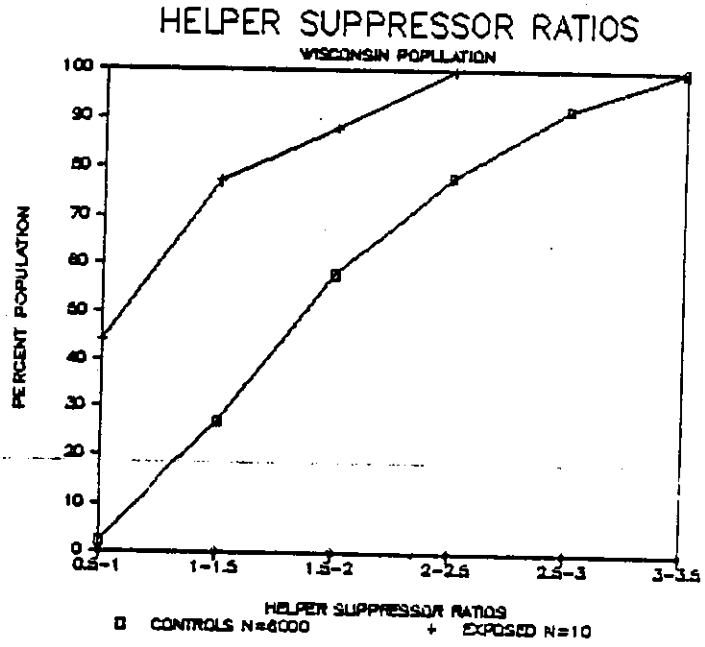

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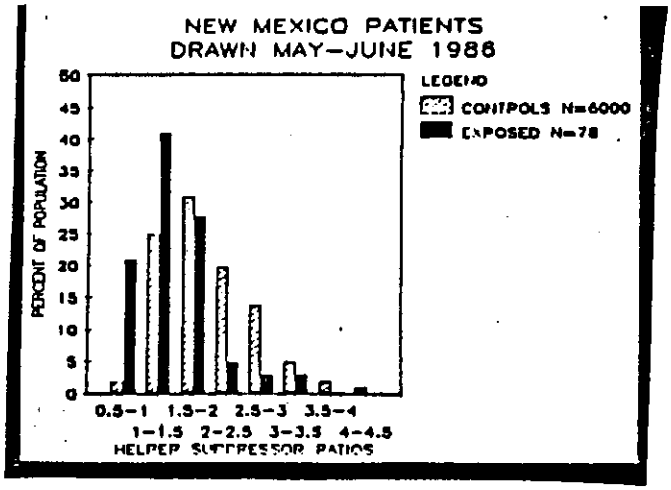

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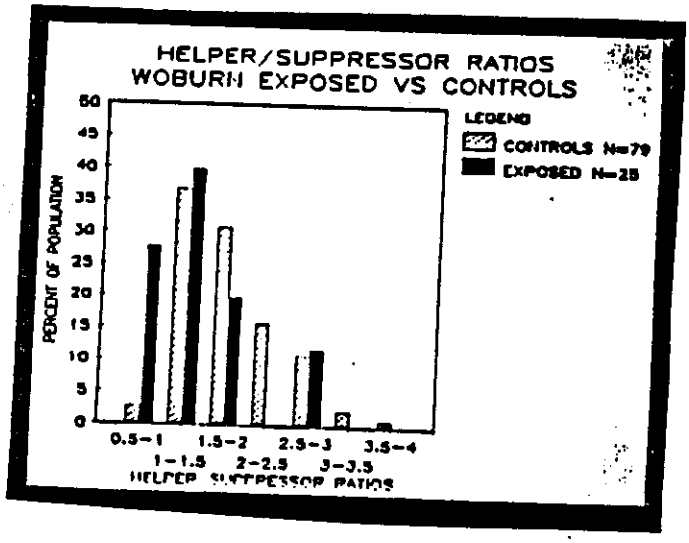

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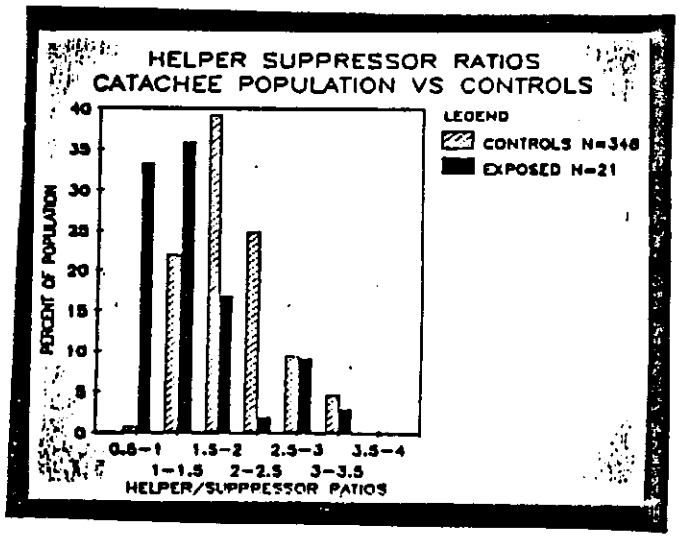

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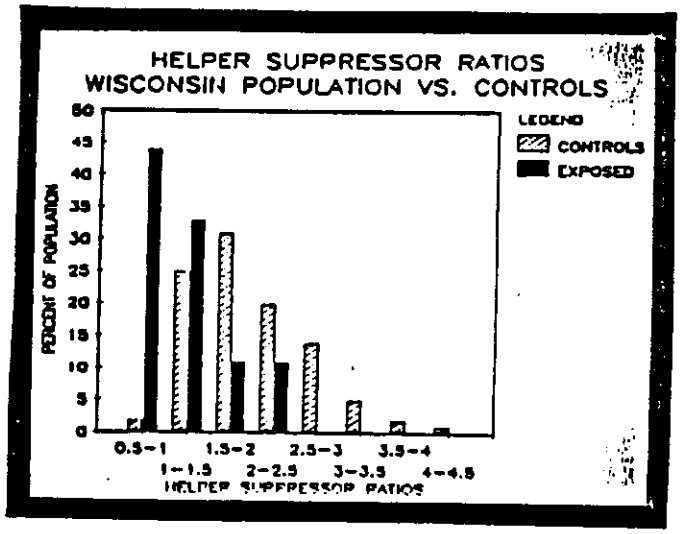

FIGURE 4

substaintial reduction of the helper/suppressor ratio as shown in figure 1. When the exposed population was compared to the controls, the difference was statistically significant (26).

Notably Hispanic female workers in this plant have a greatly increased incidence of cancer of the female reproductive tract when compared with age and sex matched controls (26).

A representative group of individuals from a population exposed primarily to poly chlorinated byphencls in their food chain and drinking water demonstrated similar abnormalities (figure 2).

A statistically significant increase in the incidence of malignant melanoma and soft tissue sarcoma was demonstrated in this population (27).

A representative sample of a population of people exposed to trichloroethylene and perchloroethylene in the city of Woburn, Mass. also demonstrated depression of helper/suppressor ratios (figure 3).

A positive correlation between exposure to the contaminated water and leukemia was demonstrated in this population (7).

A group of environmentally ill Wisconsin patients exposed to toxic chemicals in their drinking water also showed a

depressed helper/suppressor ratio (figure 4).

Human population studies demonstrate an increased incidence lymphoreticular malignancy, soft tissue sarcoma, melanoma, and genitourinary tract cancer in individuals chronically exposed to similar chemicals (17).

Reviewing the distribution of helper/suppressor ratios in exposed populations reveals a striking similarity in these parameters. This, along with the similarity in general medical symptomatology in these people, are evidence for a common pollutant as the cause of environmental illness.

HOW IS THE DIAGNOSIS MADE

Suspicion of environmental agents as the etiology of disease should be raised if a patient's symptoms have a strong neurologic component (encephalopathy and peripheral neuropathy), evidence of immune system dysfunction such as altered T and B cell functions and numbers, a history of recurrent infections (both bacterial and fungal), chronic skin rashes, arthritis or arthralgia, and neoplasm both benign and malignant, gastrointestinal symptomatology and cardiac dysrhythmias.

The diagnosis of environmental illness is made by history, physical examination, and laboratory testing. Patients may describe the abrupt onset of symptomatology associated with a specific insult. A typical comment of such an environmentally ill patient in this case is, "I have not been well since...". The triggering event can be physical trauma such as an auto accident,

viral illness such as hepatitis or mononucleosis, or exposure to noxious chemicals. Patients may also describe a gradual onset of illness over a period of months or years. These patients commonly are found to have long term low dose exposures to toxins in the air or drinking water.

Individuals may respond differently to the same toxic substance. Therefore, a population of previously normal individuals that develops a panoply of multisystem complaints at the same time can be suspected of having environmental illness. Environmental assessment can often identify a causal factor.

When taking a history, care must be taken to identify the nature of the patient's birth. Frequently individuals who were products of complicated pregnancies, such as maternal ingestion of prescription drugs such as diethyl-stilbesterol or recreational drugs and alcohol are more susceptable to damage from environmental exposure to domestic and industrial chemicals. The patient's course during the common childhood viral illnesses of measles, mumps and chicken pox are indicators of early immunologic problems. Measles or measles encephalopathy in childhood can be an indicator of diminished immune reserves in adulthood. Patients who have suffered more serious childhood viral illness such as polio and hepatitis are more susceptable to immune dysregulation as an adult. Some serious bacterial illnesses such as pertusis or pneumonias are associated with immune dysregulation in adult humans and animals (23,45,54).

A patient's inital response to normal childhood vaccinations is

important. Individuals who never developed an appropriate reaction to vaccinia ("smallpox take") may have a long standing T cell defect. Individuals who developed severe arthus reactions to diptheria- pertusis-tetanus vaccine may have long standing immune dysregulation problem. A rather detailed chronolbgic history can uncover a history of multiple viral diseases, complications in a patient's childbearing history, physical traumas such as automobile accidents, and hospitalizations for other illnesses. A history of multiple surgeries requiring general anesthetics is important since the patient's ability to tolerate such anesthetics is a clue to the presence or absence of environmental illness. Intraoperative anesthetic complications or serious difficulties recovering from the effects of the anesthetics are important historical considerations since they indicate intolerance to synthetic chemicals.

ETIOLOGIC CONSIDERATIONS:

A causal agent in environmental illness is defined as a substantial contributing factor to the development of illness. If the patient were not exposed to this agent he would not develop the disease at the same time and with the same intensity.

To accurately identify a causal agent, one must first have objective evidence of the disease. This is obtained in routine fashion by history, physical examination, and laboratory testing. Often, laboratory testing of the entire exposed population shows a significant difference in the distribution of immune parameters

when compared to controls. Therefore testing simple immunologic parameters, such as B and T cell phenotypes with subset analysis, in the entire population can reduce the need to perform more elaborate testing in single individuals whose history and symptoms are consistant with a diagnosis but whose routine laboratory results are within the expected range.

The potential causal agent must be one which can realistically initiate an illness. If a patient whose history, physical findings, and laboratory results are consistant with a diagnosis of environmental illness descirbes himself as completely well until he was exposed to the second hand smoke of a single cigarette, another potential etiologic factor would be sought. If this patient described the onset of illness after a single exposure to an intensely toxic gas which was associated with severe acute symptomatology, the toxic gas would be a candidate as the causal factor since this is an etiologic agent which can reasonably cause disease.

WHAT IS KNOWN ABOUT THE PATHOPHYSICOLOGY OF THE ILLNESS

The symptoms of environmental illness are, undoubtly, a result of numerous interactive biochemical phenomena. The biological regulatory systems, the interactive components of the neurologic, endocrine, and immunologic systems, are delicately balanced control mechanisms which involve the activity of many cells both to induce and to inhibit reactions. Like the servos in an autopilot, a series of counter forces maintain steady control.

Health depends upon the appropriate balance of these forces. Agents which can alter this balance can cause diseases such as immune and endocrine dysregulation.

A. Gross Pathology: Neurotoxic and irritant effects of chemicals produce direct pathological phenomena in target organs and may result in generalized immune and endocrine dysregulation. The medical literature is repleat with current references to the direct toxic effects of environmental agents on the neurologic and endocrine systems as well as the more subtle secondary effects on target organs (4,11,22,24,43). Since these subjects are so well covered in existing medical literature, the gross pathological mechanisms of environmental illness will not be discussed here.

B. Basic Biochemical Considerations: The basic biochemical mechanisms by which toxic environmental agents cause damage can be divided into three major catagories. These are quite similar to the effects of ionizing radiation:

1.) Free radical generation and alkylation: Toxic chemicals can cleave off electrons from proteins or cells causing them to become highly reactive (30,36). This causes the damaged moieties to become "glued" to other cells and proteins. As a result of this phenomenon the function of the damaged protein or cell is altered. This can result in severe immunodeficiency (8). In addition, these mechanisms trigger a series of immunologic phenomena.

2.) Structural alteration of antigens: The alteration of tertiary structure in damaged cells and proteins causes them to become auto-immunogenic. This can result from the expression of previously hidden antigens (hidden epitopes). Such antigens are recognized by the natural immune mechanisms as senescent and attempts are made to remove them from the body (21,31). Additionally, it has long been known that autoantibodies can be directed to either the primary and tertiary structure of antigens (3,50) and that the nature and severity of autoimmune disease is heavily influenced by these autoantibodies (51).

3.) Hapten/carrier reactions: Environmental agents such as toxic chemicals can evoke immune reactivity by generating hapten/carrier reactions. Low molecular weight toxic chemicals which, alone, are incapable of inducing an immune reaction, bind to larger molecules. This binding causes the small molecules to evoke an immune response. Subsequent exposure to the same or similar small molecule will cause a vigorous immune reaction (1,2,16).

By these basic biochemical mechanisms, toxic environmental agents can both damage and tax the immune system at the same time. The damage can be both acute and cumulative. Since many toxic chemicals are lipophyllic and remain in the body for decades their deleterious effects impact the health of an individual for long periods of time it is easy to see why toxic chemicals can be more hazardous than ionizing radiation.

CLINICAL SYMPTOMATOLOGY AND IMMUNE COMPLEXES

As a clinician, one is struck with the similarity between the symptoms of environmental illness and acute infectious hepatitis patients. Fatigue, intolerance to alcohol and cigarette smoke, and multiorgan symptomatology are symptoms shared by environmental illness and hepatitis. Of importance is the fact that hepatitis does not become symptomatic until the patient has circulating immune complexes. Since immune dysregulation leads to immune complex disease, we investigated the possibility that an immune complex mediated, complement consuming process could be partially responsible for the symptoms of environmental illness. (49). Upon evaluating a population of symptomatic patients, we discovered a significant number with elevated immune complexes (as measured by polyethylene glycol precipitation), depressed complement (as measured by C3) and elevated prostaglandin F2A suggesting that part of their symptomatology was associated with in immune complex mediated inflamatory process.

HOW IS THE DISEASE TREATED?

The best treatment for environmental illness is avoiding the offensive agent. This can often be accomplished by simple environmental alterations such as improving ventilation or wearing protective clothing and masks. Clinical improvement can often be accelorated by reducing the overall load on the immune system. This can be accomplished in most people with an allergy elimination diet. The diet is structured to remove the more common potential allergic offenders in an adult's diet. These include milk and milk prooucts, cereal grains (wheat and corn),

and refined carbohydrates (white sugar and white flour). A very common offender in individuals whose biological regulatory system has been damaged by environmental agents is the Candida Albicans organism. This ubiquitous fungus is widely recognized as an allergin responsible for multi-organ symptomatology (40). Oral administration of Nilstat (Nistatin-Lederle) in large doses or careful administration of Nizoral (Ketoconazole-Jannssen) can be very helpful. This treatment course has been described elsewhere (10,53).

Specific antigen immunotherapy-ordinary allergy treatment for dust, grass pollens, molds, tree pollens, and weed pollens can be instituted to take the pressure off the damaged immune system. In refractory cases non-specific immunotherapy with transfer factor (28) and intravenous gammaglobulin has been found to be helpful. Transfer factor has been demonstrated to enhance both helper and suppressor cell activity (28) while intravenous gammaglobulin provides the damaged immune system with idiotypic antibodies against various pathogens like virus, bacterium and fungus, as well as anti-idiotypic antibodies which reduce aberrant immune reactions (47).

HOW CAN THE DISEASE BE PREVENTED?

Prevention is the most important and simplist aspect of this problem. First and foremost we must recognize the disease exists; and that it is preventable. The simplistic explanation that it is conversion hysteria or malingering is untenable. Adequate ventilation of workplaces, utilization of appropriate protective clothing and respirators for workers, coupled with appropriate

waste disposal techniques will avoid contamination of workers and others with toxic chemicals and the spread of problems.

THE SOLUTION IS COMMON SENSE!

1. Try not to hurt anybody. Provide adequate ventilation, respirators, waste disposal, and medical screening to avoid toxic exposures.

2. If someone does get hurt, apologize by compensating him/her for their injury. Then alter the systems so that no one else gets hurt.

3. Recognize that people with environmental illness' are genuinely made ill by noxious agents from the environment. It is unclear whether these people are just different in that they are more vulnerable, or they reacting in a more acute fashion to agents which may, in the majority of the population, be responsible for otherwise unexplained chronic disease.

CAPTIONS FOR FIGURES

Figure 1. Helper/Suppressor ratios obtained by standard clinical laboratory procedures on 78 injured workers from a computer chip manufacturing plant in Alberqueque New Mexico compared with the standard laboratory control population of 6000 randomly selected assymptomatic

people (26).

Figure 2. Helper/Suppressor ratios obtained by standard clinical laboratory procedures on 21 environmentally ill patients who were domestically exposed to high levels of Polychlorinated Biphenols (PCBs) over a period of 5 to 10 years in Catachee, So. Carolina compared with the standard laboratory control population of 348 assymptomatic individuals (27).

Figure 3. Helper/Suppressor ratios obtained by standard clinical laboratory procedures on 25 environmentally ill patients from Woburn, Mass. who were domestically exposed to Trichloroethylene (TCE) over a period of 5 to 10 years compared with age and sex matched assymptomatic controls (7). This control population is not significantly different from the standard laboratory controls used in the other studies.

Figure 4. Helper/Suppressor ratios obtained by standard clinical laboratory procedures on 10 environmentally ill patients from rural Wisconson who were domestically exposed to a variety of industrial dyes, solvents, and pesticides over a 5 to 10 year period compared to the standard laboratory control of 6000 randomly selected assymptomatic people (29).

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