

Committee report

A training program directors' committee report: Topics related to controversial practices that should be taught in an allergy and immunology training program

AAAAI Training Program Directors' Committee

I. INTRODUCTION

The American Academy of Allergy and Immunology Training Program Director's Committee on Controversial Practices discussed all aspects of controversial and misused practices and therapeutic modalities. This report, which has been reviewed by all training program directors, contains an outline of topics that should be included in an allergy and immunology training program core curriculum. These included the following:

- A. A succinct definition of "controversial" and/or misused tests and/or therapeutic modalities.
- B. A list of teaching guidelines for training program directors concerning controversial practices and therapeutic modalities
- C. Comment on the standard "biomarker tests" that may be misused in the diagnosis of "environmental illness"
- D. A brief outline of major legal and medical problems that are likely to be challenges to fellows in training
- E. A brief bibliography of key articles and position papers related to scientific findings and/or discussions of a controversial nature, as a training program directors reading list on this topic

II. TEACHING GUIDELINES FOR FELLOWS (RECOMMENDED AS PART OF THE CORE TRAINING CURRICULUM):

- A. Teach proper standards and indications for use of all standard immunologic tests and treatment, including remote practice

Abbreviations used

- AIDS: Acquired immunodeficiency syndrome
- IL: Interleukin
- IL-2R: Interleukin-2 receptor
- MCS: Multiple chemical sensitivity
- sIL-2R: Soluble interleukin-2 receptor

- B. Teach necessity for controlled evaluation of all tests before their use and recognition of what constitutes an "unproven" test
- C. Teach the principles of statistical assessment and their application to outcome analysis
- D. Teach prudence in clinical test usage (selection of those tests likely to confirm or eliminate conditions suggested by history and physical examination)
- E. Teach cost-benefit analysis in selecting tests and procedures
- F. Teach proper test interpretation and cost perception in a clinical context
- G. Teach scientific evaluation of unproven and uncontrolled techniques, therapeutic modalities, and theories of human illness
- H. Define and list pitfalls of remote practice
- I. Suggested initial reading
 1. U.S. Congress, Office of Technology Assessment (OTA). Identifying and controlling immunotoxic substances-background paper OTA-BP-BA-75. Washington, DC: US Government Printing Office, April 1991. Reviews the state of the art of immunotoxicology as perceived by the Office of Technology Assessment.
 2. Selner JC, Condemi JJ. Unproven diagnostic and treatment methods. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger, JW, eds. Allergy: principles and practice. 3rd ed. St. Louis: CV Mosby, 1988:1571-97.

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Reviews the history of clinical ecology and details aspects of this movement, which the authors believe are inimical to the scientific approach and to clinical problem-solving. Reviews the potential for an environmental care unit as envisioned in the AAAI Position Statement 1991.

3. American College of Physicians. Position paper: clinical ecology. *Ann Intern Med* 1989; 111:168-78. Cites the lack of specific support for the position held by clinical ecologists and the American Academy of Environmental Medicine.
4. Salvaggio JE, Sullivan KA. Environmental chemicals and the immune system. In: Rom WN, ed. *Environmental and occupational medicine*. New York: Little, Brown & Co., 1992. Provides an overview of cellular and humoral components of the immune system and discusses the concept of immunotoxicology as it relates to environmental chemicals and their effect on immunoresponsiveness, immune deficiency, autoimmunity, and carcinogenesis.
5. JAMA Council on Scientific Affairs. *In vivo* diagnostic testing and immunotherapy for allergy. Report I, Part I of the Allergy Panel. *JAMA* 1987;258:1363-7. Report I, Part II of the Allergy Panel. *JAMA* 1987;258:1505-8. Discusses the necessity for proper clinical trials to generate reproducible results under similar conditions to adequately prove the validity of various diagnostic and therapeutic procedures.
6. JAMA Council of Scientific Affairs. *In vitro* testing for allergy. Report II of the Allergy Panel. *JAMA* 187;258:1639-43. A discussion of the large number of tests available to measure IgE antibodies is followed by an overview of the status of complement assays and tests for evaluation of immune complexes.
7. California Medical Association Scientific Board Task Force on Clinical Ecology. Clinical ecology: a critical appraisal (information). *West J Med* 1986;144:239-45.
8. Hileman B. Multiple chemical sensitivity (MCS). *Chem Engineering News*, 1991;25-42. This article summarizes the views on multiple chemical sensitivity (MCS) held by some lay persons and organizations not involved with the medical profession. It also illustrates problems with definition of terms and points of disagreement with conventional concepts in this area.

III. DEFINITIONS

In describing controversial procedures used in either diagnosis or treatment (of an allergic or

immunologic disease), it is helpful to separate those procedures that have no proven intrinsic value from those that do. In attempting to prove something in a clinical scientific sense, physicians often progress from testimony (historical data) provided by a patient to validity testing by means of a controlled double-blind experiment, with results being published in a respected peer-reviewed journal. The "unproven" procedures discussed in this report lack proof of validity by a well-designed, controlled double-blind experimental study. Unproven procedures are not capable of diagnosing or treating any specific disease. Some of these procedures are adaptations or alterations of proven procedures used in allergy diagnostic testing.

Other procedures, termed here *inappropriate*, are technically capable of detecting (or treating) something. Proponents of inappropriate forms of testing or treatment justify them by pointing out that all are used by "traditional" physicians. Allergists and immunologists must be prepared to explain to their patients the difference between appropriate and inappropriate use of a legitimate therapy. It is helpful to point out that any test or therapeutic modality can be misused. For example, x-ray films of the spine have been used by some chiropractors to "diagnose" cardiac or digestive disease. Thyroid hormone is prescribed by some physicians for treatment of fatigue or obesity in patients who have normal thyroid function. Most patients will understand that penicillin is not appropriate therapy for a viral infection, such as a common cold, when the reason is explained in simple terms. Many physicians (or lay persons) who have difficulty grasping the potential for misuse of immunologic measurements may be able to appreciate the insidious consequences of inappropriate tests or treatments such as those cited. It should also be remembered that the traditions of medicine require a physician to be a healer and a scientist. Most practitioners of inappropriate (and unproven) techniques and therapy are usually quite personable communicators who emphasize the "healing" aspects of medicine. The scientific validity of the healing process should, however, be documented before such inappropriate and unproven procedures are used in the diagnosis and treatment of allergic disease. Many of the major unproven and inappropriate tests are discussed in this article.

A. Controversial tests

1. Unproven tests

An unproven test is a procedure not based on current knowledge of pathophysiology of allergic disease(s) and lacking in scientific evidence

of efficacy in diagnosing a disease. Examples:

- a. Provocation neutralization testing (intracutaneous, subcutaneous, or sublingual administration)
- b. Cytotoxic leukocyte test
- c. Applied kinesiology
- d. Electrodiagnosis
- e. Body chemical analysis
- f. Breath analysis for chemicals

B. Unproven Tests (Theory, Method, and Critique)

1. "Provocation-neutralization testing"¹⁻⁶

- a. *Theory and method:* The patient is given a test dose of food, chemical, hormone, or allergen extract such as pollen, mold, dust, or animal dander. "Provocation" is by intracutaneous, subcutaneous, or sublingual administration of the test dose. The patient then records any and all subjective symptoms for 10 minutes after challenge. Any reported symptom is considered a positive test result. Further challenges with the same "antigen" at different doses (higher or lower) are given until the patient reports no symptoms. This is called "neutralization."
- b. *Critique:* The rationale of this type of testing is uncertain. The items used for testing are usually selected from a predetermined group of materials. These usually include such chemicals as formaldehyde, phenol, ethanol, foods, inhalant allergens, and hormones such as progesterone. Some clinical ecologists test patients with "extracts" of air, water, saline, automobile exhaust fumes, chlorine, gasoline, and other substances. Proponents of this test state that a positive response to ethanol (or phenol) indicates that the patient is allergic to all "petrochemicals." Some practitioners interpret an increase in the size of the wheal produced by intracutaneous injection (progressive whealing) as a further indication of a positive test result. A recent study by Jewett et al.⁶ with a well-designed double-blind, placebo-controlled protocol showed that responses to antigens were no different from placebo responses in 18 patients who had previously responded positively to antigen and negatively to control in an unblinded setting. The accompanying editorial by Ferguson emphasized that the results of provocation-neutralization and similar tests are based entirely on suggestion.⁷ The editorial goes on to discuss how patients and doctors can succumb to self-delusion.

2. Cytotoxic food tests and similar in vitro tests

- a. *Theory and method:* An unstained wet mount of 1 drop of whole blood or buffy coat is placed on a microscope slide precoated with a dried film of

a food extract. A cytotoxic effect (e.g., swelling, vacuolation, crenation, or other distortion of leukocytes observed microscopically) is considered indicative of food allergy. No standardization of time, temperature, pH, or osmolarity has been defined.

- b. *Critique:* Allergic reactions to foods are not caused by or associated with cytotoxicity. The procedure of the test is highly variable. Typically, the report from the laboratory states that up to 150 foods have been tested on a single blood sample. It is difficult to imagine how any technician could perform so many separate tests on the same blood sample. The cytotoxic test has been subjected to controlled double-blind studies, which have shown that results are based purely on chance and are not reproducible.^{8, 9}
3. Applied kinesiology¹⁰ (Kinesiology refers to the science of motion techniques.)
 - a. *Theory:* An allergic reaction, especially to a food, causes weakening of skeletal musculature.
 - b. *Method:* A technician *subjectively* tests muscle strength of an extremity before and after exposure of the patient to an allergen. The test exposure consists of placing a sealed glass vial containing allergen extract on the patient's skin (or clothing).
 - c. *Critique:* There is no physiologic rationale for this test and no proof of its efficacy. Nevertheless, it is widely used because of its simplicity. Patients are influenced by the believability (salesmanship) of the practitioner and accept the results of the test.
4. Electrodiagnosis
 - a. *Theory:* Allergy produces a change in electrical resistance of the skin.
 - b. *Method:* Food extract in a sealed glass vial in contact with an aluminum plate is inserted into the circuit between the skin and a galvanometer. The equipment consists of a Voll "machine" or an Interro "machine" (ESION Corp., Pleasant Grove, Utah).
 - c. *Critique:* Proponents of electrodiagnosis claim that measurement of electrical resistance at specific "allergy points" on the skin surface can be used to diagnose allergic disease. The test results are entered into a computer, which then prints out a list of allergies. Patients are frequently impressed by the appearance of a modern computerized machine, which "objectively" reports a diagnosis. They are told that this painless procedure is superior to the old-fashioned, painful skin testing procedures. There are no data to indicate the validity or efficacy of this type of testing.

5. Body chemical analysis

- a. *Theory:* All chemicals that are not normal constituents of the body or a product of its metabolism are potentially harmful. Some practitioners claim that detection of any level of these chemicals in human serum samples is indicative of abnormality. They would derive from this a cause-and-effect relationship between chemical exposure and signs and symptoms demonstrated by the patient.
- b. *Method:* Specific tests include gas chromatographic mass spectrophotometry analysis of body fluids and tissue, quantitation of chemicals in serum and other body fluids, and breath analysis. Over several years, it has become commonplace for some practitioners to order analysis of blood for panels of chlorinated hydrocarbons, volatile organic chemicals, and certain metabolites of toxins such as pesticides. These chemicals can be measured with a very high degree of sensitivity (in parts per quadrillion). Thus detection of trace amounts of many chemicals in patients and normal individuals not demonstrating any signs of disease is to be anticipated. The conceptualization of parts per million, billion, trillion, and quadrillion should be clear to trainees. For instance, one part per million would equal one banana in a string of bananas reaching from Earth to the Moon. One part per quadrillion would equal only one sheet of paper in a continuous stack of sheets packed between the Earth and the Moon.
- c. *Critique:* Some laboratories, which have been examined by state and federal authorities for accuracy in performance of these tests, have been noted to be deficient with respect to quality assurance.

Contamination of collection vials and chemicals leached from the caps on the vials being used to collect and ship samples for analysis are the primary sources of error in the assays. The average levels reported by certain laboratories are approximately 10 times greater than those detected in research laboratories of the Agency for Toxic Substances and Disease Registry and the Centers for Disease Control.

According to sources at the Centers for Disease Control and the Agency for Toxic Substances and Disease Registry, there is currently no laboratory within the United States that does not have the same problems in sample analysis that are here described. Further, there is no database of trace levels of chemicals in groups of individuals with and without signs and symptoms of disease.

Trainees should be acquainted with studies on the possible effects of low-level chemical exposure in human beings. Medical judgment on the theoretic effects of such exposure should be dictated by the science rather than the politics involved. For example, although this subject is controversial, dioxin has, according to some reports, not been conclusively proven to be responsible for the myriad symptoms for which veterans exposed to this defoliant during the Vietnam War are presently being compensated.¹¹

Likewise, formaldehyde, which has been classified as a probable carcinogen by the Environmental Protection Agency and is being regulated as such, has not been determined to be carcinogenic in human beings by the World Health Organization's Task Force on Formaldehyde or by the current body of scientific literature.

6. Breath analysis for chemicals

- a. *Theory and method:* Detection of chemical(s) in breath sample analysis provides evidence of exposure and may correlate with a disease process. In the diagnosis of chemical exposure, a database has been developed, which provides an indication of chemical exposure, provided that the time of exposure is known. Such studies can be performed at the Research Triangle Institute in Triangle Park, North Carolina.
- b. *Critique:* These tests require the presence of the patient because there is no methodology for providing a sample from a distant source.¹² Thus this test is primarily impractical rather than unproven.

It should be noted that breath analysis can be used to diagnose certain diseases, and in these cases it is not an unproven test. For example, hydrogen gas analysis after ingestion of lactose is an accepted procedure for diagnosing disaccharidase deficiency.

7. Commercial hair analysis (Although this procedure is grouped with unproven procedures, it is also an example of inappropriate testing.)

- a. *Theory and method:* Human hair specimens are analyzed for content of multiple minerals to predict nutritional or trace element abnormalities.
- b. *Critique:* Serious questions have been raised about the accuracy of hair analysis in predicting nutritional or trace element abnormalities. An example of the questions that have been raised with respect to this methodology is the following 1985 abstract from the *Journal of the American Medical Association*.¹³

Hair samples from two healthy teenagers were sent under assumed names to 13 commercial laboratories performing multimineral hair analysis. The reported levels of most minerals varied considerably between identical samples sent to the same laboratory and from laboratory to laboratory. The laboratories also disagreed about what was the "normal" or "usual" for many of the minerals. Most reports contained computerized interpretations that were voluminous, bizarre, and potentially frightening to patients. Six laboratories recommended food supplements, but the types and amounts varied widely from report to report and from laboratory to laboratory. Literature from most of the laboratories suggested that their reports were useful in managing a wide variety of diseases and supposed nutrient imbalances. However, commercial use of hair analysis in this manner is unscientific, economically wasteful, and probably illegal.

The indiscriminate use of these methods can delay proper diagnosis and treatment.

8. Inappropriate tests

An inappropriate test is a procedure of diagnostic or therapeutic value for certain clinical conditions, as demonstrated by scientific evidence, but without value for the particular application chosen.

- a. Measurement of IgG antibodies and circulating immune complexes to foods in diagnosis of food allergy*
- b. Measurement of lymphocyte subsets, immunoglobulins, or other immunologic parameters in patients with alleged "environmental or ecologic disease" who have no symptoms or signs of immune deficiency or autoimmune disease
- c. Measurement of pulse rate changes for diagnosis of chemical, food, or related "allergic" conditions
- d. Chamber challenge procedure of an uncontrolled nature without objective measurements of response or with the use of irritant test doses of the putative offending agent^{14, 15†}
- e. Analysis of vitamins, minerals, or amino acid

*There has been a proliferation of advertising for measurement of IgG antibodies reactive with food antigens in the diagnosis of alleged food allergy.

†These procedures are recognized for specificity and sensitivity when used under proper and controlled laboratory conditions. This requires: (1) baseline assessment of the patient, (2) double-blind control procedure (placebo and putative offending agent), (3) control of ambient background exposures, (4) documented chemical delivery systems, (5) patient exposure monitoring, (6) patient response monitoring, and (7) outcome analysis.

content of urine or hair analysis for diagnosis of "environmental illness."[‡]

C. Particular forms of unproven therapy

1. Neutralization therapy

- a. *Theory and method:* Neutralization of allergic symptoms is an extension of provocation-neutralization testing. After completing the testing, the patient is given a vial of each antigen at a concentration that "neutralized" the symptoms provoked during the testing. Neutralization treatment (also called relieving therapy) is self-administered by the patient either sublingually or by injection. It is recommended to relieve symptoms once they occur or to prevent symptoms by administration before an expected encounter with an antigen in the environment.

- b. *Critique:* A number of theories have been proposed to explain neutralization of allergic symptoms, but none "make sense" immunologically (or pharmacologically). There have been no studies showing short-term or long-term efficacy of this "therapy." The suggestive nature of this therapy is illustrated by the fact that patients who believe the treatment works will report that *any* symptom can be relieved.^{6, 16}

2. Rotation diets

- a. *Theory and method:* The rotation diet (also called Rotary Diversified Diet) consists of *not* eating the same food more often than once every 4 or 5 days. This is based on a theory that the patient is allergic (or intolerant pharmacologically) to most or all foods and that eating the same food too often increases sensitivity (or reactivity) to that food and to other allergens.
- b. *Critique:* The rotation diet has never been tested for efficacy and thus has no sound scientific basis.

3. Acupuncture¹⁷

- a. *Theory and method:* Acupuncture has been practiced for thousands of years in China. The methodology is well known. It may have an accepted place as a therapeutic modality in control of some types of pain. It is, however, difficult to understand the rationale of acupuncture in relieving allergic symptoms other than to postulate that it effects release or inhibition of neuropeptides and neutral endopeptidases, which in turn affect mast cell activity. This possibility remains to be proven.

‡Many advanced technologies can be used in an attempt to analyze nutritional status or to identify the presence of heavy metals or other toxins (see section on orthomolecular therapy).

- b. *Critique:* Acupuncture has never been properly tested for efficacy in treating allergic disease.
- 4. Orthomolecular therapy
 - a. *Theory and method:* Orthomolecular therapy generally refers to the use of supplements (vitamins, minerals, enzymes, amino acids), often administered in large quantities parenterally or orally. These substances are recommended for use on the basis of clinical fiat or results of serum or urine analysis for their quantity, based on a theory that they will correct alleged or presumed deficiencies and possibly cure diseases (e.g., high-dose vitamin therapy in cancer).
 - b. *Critique:* The utility of these interventions has not been subjected to carefully controlled trials. With regard to vitamin, mineral, and amino acid supplement therapy, it should be remembered that the health food industry has successfully lobbied for laws that classify their products as foods or nutritional supplements, rather than biologic agents or drugs. This affords considerable advantages to an enormous industry that is not subject to Food and Drug Administration and related regulations of its products.
- 5. Homeopathic remedies
 - a. *Theory and method:* Homeopathic remedies consist of the therapeutic administration of extremely dilute extracts of a variety of animal and plant substances. Some have known pharmacologic effects, but not at the low dose used. Patients will sometimes be given as many as 40 or 50 different extracts each day. This is explained as an effort to achieve homeostasis.
 - b. *Critique:* There is no evidence, based on properly controlled studies, that homeopathic remedies are efficacious in treating allergic disease.
- 6. Mercury amalgam removal
 - a. *Theory and method:* For at least a decade, certain physicians and dentists in the United States have claimed that some individuals have a very low tolerance for mercury either because of allergy or some undefined hyperreactive state. Their target is the silver-mercury amalgam used in dental fillings for the last 150 years. Hypersensitivity to the mercury in such fillings has been blamed for a wide range of symptoms and medical conditions of uncertain cause. Such claims have led to the removal of a substantial number of silver-mercury amalgam fillings.
 - b. *Critique:* In most cases the multiplicity of somatic complaints exhibited by those individuals with a low tolerance for mercury are similar to those noted in MCS syndrome. It has been claimed that silver-mercury amalgams are a

causative agent in multiple sclerosis. Such claims have been supported only by anecdotes that were publicized during a CBS "60 Minutes" television program in December 1990.

There is no scientific foundation for such claims. The occasional patient with allergy to mercury has allergic eczematous contact dermatitis. There is no evidence that individuals are otherwise affected by silver-mercury amalgams.¹⁸

D. Particular forms of inappropriate therapy

- 1. Multiple food elimination diets and multiple chemical avoidance
 - a. *Theory and method:* Diets and avoidance methods fall into two categories: (1) elimination of multiple foods based on the diagnosis of multiple food allergy with an unproven method^{7, 19} and (2) elimination of multiple foods from the diet based on the concept that this will in some mysterious way "boost the immune system" (usually in conjunction with dietary supplements).
 - b. *Critique:* Elimination of multiple foods, based on unproven diagnostic methods or on the concept that the immune system will be "boosted," is without scientific basis. There is no proof of efficacy of these approaches. Fortunately, most patients do not adhere to restrictive elimination diets very long. Those who do, however, can be subject to harmful nutritional and psychologic effects.^{20, 21*}
- Likewise, the diagnosis of MCS often leads to avoidance of food additives, solvents, pesticides, and anything else that the patient considers to be a "chemical." In extreme examples, the patient will retreat to a rural or mountainous locale to live like a hermit or remain trapped inside a "safe" house. The psychologic harm caused by such a recommendation is obvious. Once a patient accepts the concepts of MCS and follows the recommended course, the outcome may be an environmental cripple with devastating effects on patient, family, and friends.
- 2. Anti-*Candida* drugs (*Candida* hypersensitivity syndrome)

*Data are accumulating on relative intolerances that can occur to some foods. Two examples are (1) *histaminiasis* in which drugs or food may affect the level of diamine oxidase in the gastrointestinal tract, which in turn influences the absorption of histamine from histamine-containing foods such as fish and (2) *O methyltransferase deficiency*, an enzyme deficiency, which can render one highly reactive to orally ingested ephedrine compounds.

- a. *Theory*: This treatment is based on the hypothesis that *Candida albicans*, as part of the normal body flora, releases an immunotoxin, causing multiple symptoms.^{22, 23}
- b. *Method/diagnosis*: The diagnosis is made by questionnaire. No abnormal physical signs or laboratory test results have been defined in this condition.

The treatment consists of three regimens: a sugar-free, yeast-free rotation diet, low-dose oral administration of nystatin, and occasional use of ketoconazole or a similar anti-*Candida* agent. *Candida* antigen is often injected into these patients. Delayed reactions to intradermal tests with *Candida* antigen are interpreted as abnormal, and injections are initiated on that basis. These injections result in marked local reactivity at the site of injection.

- c. *Critique*: *Candida* hypersensitivity, or "the yeast connection," is a currently popular diagnosis, but in reality, it is a resurrection of the old-fashioned "autointoxication" theory that was popular in the early 1990s. In this case the normal colonization of the gastrointestinal tract, vagina, or moist body surfaces with small numbers of *C. albicans* is alleged to release a toxin (unidentified) that damages the immune system. (This is unproven.) This damage leads to multiple symptoms identical to those of environmental illness. Many clinical ecologists attribute illness to a combination of environmental chemicals, foods, and *C. albicans*, all acting together or synergistically in the same individual (see *Theory* and *Critique* under 3. Clinical Ecology and Environmental Illness).

The patient can allegedly self-diagnose the condition by completing a questionnaire or history form. The list of potential symptoms is so inclusive that virtually all patients find that they fit the criteria for diagnosis. There is no scientifically valid basis or proof of diagnostic efficacy for this approach.

3. Clinical ecology and environmental illness

- a. *Theory*: The concept of environmental illness is based on the premise that a wide range of synthetic chemicals damage the immune system, thereby causing multiple chemical and food sensitivities. Symptoms allegedly resulting from low-level long-term exposure to synthetic and natural organic and inorganic environmental chemicals have led to the coining of terms such as *environmental illness*.

Synonyms for this type of environmental illness are *chemical hypersensitivity syndrome*, *chemically induced immune dysregulation syn-*

drome, *total allergy syndrome*, *ecologic illness*, *environmental hypersensitivity disorder*, and *twentieth century disease*. These terms have been used by some physicians to describe multisystemic protean symptoms, allegedly caused or exacerbated by exposure to a wide range of industrial and domestic chemicals, atmospheric pollutants, exhaust fumes, cigarette smoke, insecticides, preservatives, and related environmental contaminants. Other substances have also allegedly produced multisystemic symptoms secondary to occupational exposure. These diagnoses are often made in the absence of objective signs of disease as determined by physical examination and absence of abnormal physiologic or laboratory test results.

The concepts of clinical ecology involve the following four phenomena: total body load, overload, masking, and spreading. Clinical ecologists may use these descriptive and often colorful terms and concepts because of lack of scientific data or in-depth understanding of pathogenic mechanisms. In simplistic terms, clinical ecologists draw an analogy between the immune system and a container, such as a barrel. They propose that the immune system has a limited capacity—like a barrel—for handling antigens (encountered by the environmental exposure). If someone consequently experiences a symptom—any symptom related to any organ system—this indicates that the barrel is filled to overflowing. This explanation, although totally unsubstantiated, convinces patients to follow restrictive diets and avoid contact with environmental agents. Two additional concepts—the "spreading phenomenon" and "masking"—have been advanced by clinical ecologists to explain worsening or improvement of symptoms. The spreading phenomenon alludes to the belief that exposure to one antigen causes the patient to be allergic to other unrelated antigens. This concept is used to explain worsening of symptoms. The term *masking* is used to express the belief that eating the same food on a regular basis *eliminates* symptoms induced by that food. This is a convenient concept to explain why the patient's condition might be improving.

The above concepts and terms are strange and totally without foundation. It should be remembered, however, that many other strange, unexplained phenomena may become manifest in allergic individuals, such as the bronchial hyperreactivity to multiple irritants that occurs in association with late-phase in-

flammation and the anaphylactic or urticarial reactions that occur in some individuals who exercise vigorously after eating a certain food but do not occur after exercise alone or after ingestion of the food alone.

- b. *Diagnosis:* This is usually based on history, provocation-neutralization testing, and determination of serum or fat chemical levels (e.g., pesticides, chlorinated hydrocarbons, and volatile organic chemicals).
- c. *Treatment:* Therapy consists of neutralizing sublingual "drops" or subcutaneous injections, chemical avoidance, and detoxification strategies, which include sauna, exercise, massage, and dietary supplements with anti-oxidants, in addition to rotational diets.
- d. *Outcome:* Patients generally become environmentally crippled or experience unnecessary anxiety and stress.
- e. *Critique:* In recent years, investigators have critically examined groups of patients diagnosed by clinical ecologists as having environmental illness.²⁴ These patients were found to constitute a heterogeneous group. There was no consistent history, although a majority had long-standing multiple unexplained symptoms. There were no abnormal diagnostic physical findings and no abnormal diagnostic laboratory test results. Environmental illness is in essence not an illness but rather a belief that an illness exists. The condition is "declared" rather than diagnosed. One reason for the current popularity of clinical ecology is widespread public awareness of the immune system because of public awareness of acquired immunodeficiency syndrome (AIDS). In fact, environmental illness has been called *chemical AIDS* by some proponents. Indeed, there is a growing perception among the public at large that *any* illness, symptom, or discomfort is likely to be caused by immune system failure.²⁵

On December 10, 1991, the American Medical Association House of Delegates approved a report on clinical ecology submitted by the Council on Scientific Affairs. The major recommendation, as reported in *AMA News* (December 1992, 23/30, p. 25) is this: "Those who support a new test, procedure or treatment, must prove, by appropriate controlled trials, that it is effective for the purposes for which it is used. The burden should not be shifted to opponents to prove that a new test or therapy is invalid."

4. MCS syndrome

Another syndrome, MCS (supposedly distinct from environmental illness but with con-

siderable overlap), has also been proposed.²⁶ Criteria for the diagnosis of MCS are that no accepted test of physiologic function can correlate with symptoms and that the disorder must be acquired in relation to documentable environmental exposure. As in the case of environmental illness, the lack of objective evidence of disease as determined by physical examination, laboratory test results, or organ system disease casts doubt on the validity of MCS as a diagnostic entity. Symptoms manifested by individuals with alleged MCS, which must be elicited by exposure and must be demonstrable to others, are protean in nature and can involve the nervous, endocrine, genitourinary, immune, muscular, and other systems. Chronic fatigue, depression, and symptoms suggestive of a neurologic component such as headache, dizziness, and poor concentration are often prominent. In contrast, a patient with evidence of cerebral atrophy (associated with long-term solvent or pesticide exposure) demonstrated by magnetic resonance imaging or positron emission tomography would not be diagnosed as having MCS. Little is known about the pathophysiology of these environmental illness and MCS symptom complexes, but many possible mechanisms have been invoked to explain their presence. Among these are free radical generation, the action of environmental chemicals as haptens, or the ability of such chemicals to damage tissues in the form of circulating immune complexes.

We all have much to learn. All sides of every issue should be examined; it is best to maintain an open mind about environmental illness and MCS. As presently used, however, the terms *environmental illness* and *MCS* do not appear to define a disease per se but rather to focus on a list of wide-ranging subjective symptoms associated with exposure to an even wider range of environmental chemicals and related agents.

5. Psychopathologic characteristics of patients with environmental illness and MCS

Several personality types are typically characteristic of patients with environmental illness or MCS syndrome. These include suggestible patients, true believers, and antiestablishment advocates. These individuals may manifest major psychologic features including anxiety and depression, somatization, conversion, and phobia. Many patients have long-standing histories of psychosomatic complaints and hypochondriasis. Their symptoms are often consistent with psychiatric disorders.²⁷⁻²⁹ Several studies

document the high rate of psychopathologic conditions among patients diagnosed with environmental illness.³⁰⁻³⁴

There is also a strong element of fear and even phobia connected with attitudes about the environment. The patient with alleged environmental illness is usually not willing to accept a psychologic explanation for symptoms. It should be emphasized that very little is understood about psychologic factors operable in these patients. There is a need for more research and more accurate information in this area.

E. Remote Practice of Allergy

1. Definition

The remote practice of allergy refers to the diagnosis of an allergic condition and of specific allergic sensitivities on the basis of results of tests performed in a reference laboratory without the benefit of a clinical history and 17 physical examination to provide a proper context for interpretation of such test results. The *proper* diagnosis of any allergic disease in an individual patient is made by a physician knowledgeable about principles of allergy and immunology who uses a sequential process of history, physical examination, and in vivo or in vitro test procedures.

2. Analysis of results

Results of tests, especially those for specified IgE antibody-mediated sensitivities, must be interpreted in the context of the results of the patient's history and physical examination. Based on all of these considerations, a diagnosis may be made and treatment prescribed. The potential deficiencies of a variety of in vitro tests, available commercially, must be appreciated. There is a tendency for some medical practitioners to depend entirely on the results of standard diagnostic tests without analyzing the clinical significance of these tests as they relate to the patient's symptoms. This practice may lead to unnecessary treatment at best and dangerous treatment at worst.

F. Misuse of "Biomarker" Tests

1. Definition

Immunotoxicology is the discipline concerned with the selective toxic effect of xenobiotic substances on the cellular and humoral components of the immune system. Exposure to toxic substances at dose levels below those that induce severe general organ toxicity may theoretically lead to stimulation (leading to hypersensitivity reactions or autoimmunity) or suppression of the immune system (leading to infection or neoplasia). Because of the

heightened awareness of potentially toxic substances in the environment, there is great interest in detecting the effects of such substances on the immune system.

2. Tiered testing

The Subcommittee on Immunotoxicology of the Committee on Biologic Markers, National Research Council, has proposed a tiered testing regimen that may be used to assess patients with known or suspected exposure to an immunotoxicant.³⁵

- a. Tier 1 procedures (which may be applied to all persons exposed to immunotoxicants) include measurement of humoral immunity; lymphocytes (enumeration of T and B cells and surface analysis for CD3, CD4, CD8, and CD20); tests of cutaneous delayed-type hypersensitivity; and assessment of autoantibody titers (to erythrocytes or nuclear antigens).
- b. Tier 2 procedures may be applied to all persons with abnormal Tier 1 test results and to a fraction of the total exposed population. These tests include the induction of a primary antibody response to protein and polysaccharide antigens; assessment of proliferative response to mitogen and antigens; induction of a primary delayed-type hypersensitivity reaction; enumeration of natural killer cells and monocytes; and application of additional T-cell and B-cell markers (CD5, CD11, CD16, CD19, CD23, CD64; class II major histocompatibility complex on T cells; measurement of serum levels of cytokines and of shed or secreted cellular activation markers and receptors; class I and II major histocompatibility complex typing).
- c. Tier 3 tests may be applied to those with abnormalities in Tier 2 test results and to a random fraction of the entire population in Tier 2. An example of these tests is the performance of nonspecific killing of a tumor cell line to test for natural killer cell function. Optimum interpretation of the tiered tests would require information from studies in which, for example, workers exposed to potentially toxic chemicals are followed up sequentially to detect evidence of immune system dysfunction.

The application of portions of these test batteries to persons who allege that injury has resulted from exposure to toxic substances has led to misuse of biomarker assays. Studies of lymphocyte surface markers, in which monoclonal antibodies to various clusters of differentiation (CD) antigens and flow cytometry are used, have been performed on these persons; minor departures from normal values have been considered evidence of injury to the immune sys-

tem. These interpretations have ignored the wide range of normal values; the variations in normal ranges in different laboratories; the influence of age and sex; the presence of concurrent viral infections; cigarette smoking; the effects of drugs, stress, or associated diseases; and the time of day blood samples were obtained.^{36, 37} Also ignored has been the lack of standardization of flow cytometry, which is only now under consideration. Perhaps most importantly, these interpretations have been made in the absence of a complete history and physical examination of the individual alleging injury. Clinical evaluations should not be based on the results of isolated *in vitro* assessment of quantity and function of immune system cellular components without consideration of the above variables and without knowledge of the complete case history and results of physical examination. This is especially true when a test subject with alleged environmental injury has no symptoms characteristic of immune deficiency or no abnormal signs as determined by physical examination, as is often the case. Some patients have been misdiagnosed as having various forms of immune dysregulation, immune dysfunction, or even chemical AIDS in the absence of evidence of overt clinical disease on the basis of such cellular, immunologic, quantitative, and functional assays. If the previously enumerated confounding variables are not considered and if minor deviations from the norm are interpreted as evidence of disease without sound clinical judgment, erroneous diagnoses will be made on the basis of laboratory tests results alone.

Cytokine quantitation has also been used by some as a diagnostic aid in alleged environmentally induced immunoregulation disorders.³⁷ Interleukin-2 (IL-2) production has been measured in a variety of immunodeficiency, autoimmune, and related diseases. Marked increases of IL-2 have been noted in certain autoimmune and related inflammatory diseases, and production has been impaired in a variety of immunodeficiency diseases.^{38, 39} Plasma and urine IL-2 receptor levels are also increased during renal allograft rejection and in variety of inflammatory and infectious diseases. Normal ranges vary widely, and random measurement in a given patient would neither support nor refute the presence of illness. There are no studies that show altered production of cytokines in individuals exposed to environmental chemicals.

The IL-2 receptor (IL-2R) and its β -chain

component, often referred to as the high-affinity receptor or soluble IL-2R (sIL-2R), have also been actively studied with the use of monoclonal antibodies. There is, however, no evidence for increased sIL-2R levels in individuals with alleged environmental illness. Among the conditions that have been associated with sIL-2R release are autoimmune diseases, graft-versus-host reactions, infectious and parasitic diseases, lymphoreticular malignancies, multiple sclerosis, and AIDS.⁴⁰⁻⁴³ In certain autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, high serum levels of IL-2 and IL-2R have correlated with disease activity.

3. Detection of antinuclear antibodies

Another example of the misuse of biomarker assays arises from detection of antinuclear antibodies in serum of persons allegedly exposed to immunotoxins. The presence of such antibodies has been interpreted as evidence of the induction of autoimmune disease, often without any evidence of disease as determined by history and physical examination. These interpretations have ignored findings that a serum sample from approximately 35% of normal persons will yield a positive test result for antinuclear antibody, if this serum sample is examined at dilutions of less than 1:10, and that antinuclear bodies in higher titers are found in approximately 4% to 6% of apparently normal older individuals.⁴⁴ At present, however, there is no sound evidence that autoantibodies are operative in the pathogenesis of human diseases associated with exposure to environmental chemicals or pollutants or that autoantibodies are in fact induced by such exposure in human beings.

Trainees should be able to recognize that the demonstration of autoantibodies *per se* does not necessarily indicate autoimmune disease. The titer and pattern of certain antinuclear antibodies may be correlated with objective signs and symptoms of disease activity and other factors (e.g., age), but the major indication for performing these tests is to aid in the diagnosis of various connective tissue diseases.

4. Conclusions

At this time, there is no sound evidence that levels of cytokines, ILs or IL receptor expression and function (such as IL-1, IL-2, IL-2R, or other ILs) are increased or decreased in patients with alleged environmental illness, although such assays are often performed by labo-

ratories associated with clinical ecologists. It is, however, reasonable to anticipate that development of assays for many of the ILs and their receptors may become important in the diagnosis and therapy of autoimmune, allergic, neoplastic, and infectious diseases.

IV. MEDICAL AND LEGAL PROBLEMS THAT FELLOWS WILL LIKELY ENCOUNTER

A. Involvement in "Toxic Tort" Litigation

Toxic torts are described as civil wrongs including alleged harm resulting from exposure to or contact with occupational, environmental, or pharmaceutical agents. In these cases the plaintiff must prove liability, causation, and damages (including need for future medical surveillance, fear of future disease, and the reasonableness and necessity of past medical treatment). A book entitled *Galileo's Revenge: Junk Science in the Courtroom*, by Peter W. Huber (Basic Books, 1991) is recommended for those interested in tort liability.

B. Working with Other Groups to Prevent Occupational and Environmental Related Illnesses or to Treat Patients with Such Illnesses

In these endeavors, the physician must often develop working relationships with the following persons and groups:

1. Corporate doctors of medicine
2. Plant managers
3. Corporate directors
4. Environmental groups
5. Regulatory agencies
6. Plaintiff and defense attorneys

C. Defining and Understanding the Diagnosis and Treatment of Patients with Suspected or Alleged Chemical-Induced Environmental Injury

These include, among others, patients with alleged environmental illness, MCS, *candidiasis* syndrome, and chemical AIDS.

D. Legal Education

In view of the above, it is recommended that program directors consider arranging for a competent, respected lawyer who is conversant with controversial tests and therapy to educate fellows on the legal aspects of toxic torts. A workshop(s) at future academy meetings (or other meetings) to discuss all aspects of this topic would also be of benefit to fellows in training.

V. SOURCES OF INFORMATION

- A. American Academy of Allergy and Immunology

- B. American College of Allergy and Immunology
- C. Asthma and Allergy Foundation of America
- D. American Medical Association
- E. American College of Physicians
- F. Health Care Financing Administration
- G. National Council Against Health Fraud

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