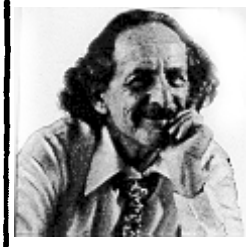
Essays of an Information Scientist, Vol:8, p.140-150, 1985
Current Contents, #15, p.3-13, April 15, 1985



Current Comments®

EUGENE GARFIELD
INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST., PHILADELPHIA, PA 19104

# Allergies Are Nothing to Sneeze At. Part 2. Diagnosis and Treatment

Number 15 April 15, 1985

In Part 1, we discussed the etiology and epidemiology of allergy.[1] This second part will focus on the diagnosis and treatment of allergies. Diagnosing an allergy is much like detective work. The physician gleans clues from the case history, and confirms the clinical impression by using allergy tests that help determine the cause of the patient's problems. Recent progress in understanding the basic mechanisms of the allergic reaction has made diagnosis, as well as controlling the unpleasant symptoms, somewhat easier.

Allergic complaints are among the most common reasons patients seek the advice of a physician in industrialized countries. While some symptoms of allergy are not difficult to detect, many may mimic numerous other physical problems. For this reason, the diagnosis and treatment of allergic disorders can sometimes challenge even the most experienced clinician. But unfortunately, recognizing allergic disorders is often bungled by general practitioners. As medical detectives they are about as competent as Inspector Clouseau of *Pink Panther* fame.

## Diagnosis

The first step in diagnosing allergy is through the case history and the patient's observations on the possible causes of the allergy symptoms. Seasonal disorders of immediate hypersensitivity generally are not difficult to diagnose. However, many allergies occur year-round. These are usually more difficult to diagnose than seasonal disorders. For example, A. Pécoud and colleagues, Immunology and Allergy Division, Central Hospital, University of Vaudois, Lausanne, Switzerland, studied 81 patients with year-round symptoms of asthma or rhinitis (inflammation of the mucous membrane of the nose). They found that in taking only case histories physicians miss about 40 percent of the allergens responsible for the symptoms.[2] However, this would vary considerably according to the reliability of the original history.

Fred M. Atkins and Dean D. Metcalfe, Allergic Disease Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, Maryland, noted that three criteria must be met for the diagnosis of allergy: identification of the allergen; demonstration of a relationship between exposure to the allergen and the resulting symptoms; and discovery of the immunologic mechanism involved.[3]

Skin testing is the standard means of determining the offending allergen. The test produces a small-scale allergic reaction by exposing the patient to minute amounts of potential allergens either scratched or injected into the epidermis, or outer layer of the skin on the patient's

forearm or back. A positive reaction produces a wheal, or whitish lump, with a reddish circle within 15 minutes.

Skin testing, however, is not without its drawbacks. For example, Harold S. Nelson, Allergy-Immunology Service, Fitzsimons Army Medical Center, Aurora, Colorado, noted that skin testing requires the patients' withdrawal from prescribed or over-the-counter antihistamines that may be used in treating their allergy symptoms, some physical discomfort to the patient, and a remote risk of anaphylaxis, or severe allergic reaction.[4]

Provocation testing is occasionally used if inhalant or food allergy is suspected. Atkins and Metcalfe note that one of the provocation tests, the oral food challenge, may be used in diagnosing food allergy when previous reactions to a suspected food have not been life threatening.[3] Provocation tests require elimination of all suspected foods for a two-week period. If the patient is symptom free, a suspected allergen is administered to provoke a response.

The diagnosis of clinical allergy became a laboratory science soon after the discovery in 1967 by the Ishizakas, then of the Children's Asthma Research Institute and Hospital, Denver, Colorado, that immunoglobulin E (IgE) is the antibody responsible for immediate hypersensitivity reactions.[5] In 1967, Leif Wide and colleagues, Department of Clinical Chemistry, University Hospital, Uppsala, Sweden, developed an *in vitro* test for measuring allergen-specific IgE antibodies.[6] The test, known as the radioallergosorbent (RAST) technique, soon became common for laboratory diagnosis of allergies. Since its publication, the paper has become a *Citation Classic*™ because, as Wide indicated, "RAST has become extensively used as a test for diagnosis of allergy and for quantitation of allergen-specific IgE."[7]

The RAST test measures the amount of circulating allergen-specific IgE in the patient's blood serum and is an *in vitro* analogue of skin testing. Small samples of the patient's serum and various potential allergens, incubated with radioactively labeled antibodies, are put into a gamma counter, an instrument used for detecting the radioactivity emitted. The radioactivity detected is an indirect measure of allergen-specific antibodies. This is a simplified description of a complex procedure for detecting radioactivity in each of several fractions.

In a review of the diagnosis of immediate hypersensitivity, Bernard Hess Booth III, Department of Medicine, University of Mississippi, Jackson, concluded that RAST testing is about as sensitive as the skin-prick test.[8] The RAST also has several advantages. It requires less of the patient's time and is not influenced by drugs used to control allergy symptoms that the patient may be taking. And perhaps most importantly, there is no risk of anaphylaxis.

The RAST is, however, not without criticism. According to S. Allan Bock, National Jewish Hospital and Research Center, and the University of Colorado Health Science Center, Denver, the fact that the RAST measures circulating antibodies and not those bound to effector cells that release the chemical mediators of allergy makes it less accurate than skin testing.[9] The RAST is also significantly more expensive than skin testing and the results are not immediately available.

Another laboratory method for allergy testing is the enzyme-linked immunosorbent assay (ELISA) developed in 1972 by E. Engvall and P. Perlmann, then of the Department of Immunology, Wenner-Gren Institute, University of Stockholm, Sweden, to determine immunoglobulin G (IgG) concentrations.[10] This method differs from the RAST in that it uses an enzyme label rather than a radioactive tag for measuring IgE in blood serum. The ELISA was later adapted to detect IgE antibodies, and

P.V. Subba Rao and colleagues, Department of Biochemistry, Indian Institute of Science, Bangalore, and National Institute of Allergy and Infectious Diseases, NIH, found that the ELISA has the same potential as the RAST to identify allergen-specific IgE.[11] Majid Ali and colleagues, Holy Name Hospital, Teaneck, New Jersey, note that the ELISA method has several advantages over the RAST. The ELISA has a diagnostic efficiency for detecting specific IgE similar to the RAST. However, the ELISA method does not require radioactive material, and the laboratory instruments that are used generally are less expensive.[12]

In a review of controversial practices in allergy, Michael H. Grieco, Department of Medicine, Columbia University College of Physicians and Surgeons, and the R.A. Cooke Institute of Allergy, St. Luke's-Roosevelt Hospital Center, New York, reported that RAST testing is more expensive than skin testing and does not offer proportionately greater information for clinical diagnosis.[13] In a study comparing RAST and skin tests, H.A. Sampson and R. Albergo, Divisions of Allergy, Immunology, Pulmonary Diseases, and Dermatology, Duke University Medical Center, Durham, North Carolina, concluded that the RAST test is best reserved for patients for whom skin testing is not possible. Such patients would include those who cannot discontinue allergy medication, those with skin problems that would make skin testing difficult, and patients who risk anaphylactic reaction with skin testing.[14]

However controversial, the important new role of laboratory diagnosis of allergy is reflected in the 1983 decision of the American Board of Allergy and Immunology, American Board of Pediatrics, and American Board of Internal Medicine to jointly sponsor a certification examination for internists and pediatricians in diagnostic laboratory immunology. The examination will be conducted under the aegis of the American Board of Medical Specialties. According to Peter F. Kohler and colleagues, American Board of Allergy and Immunology, Philadelphia, these physicians will be concerned with the laboratory aspects of immunology and their application to the diagnosis and treatment of human disease, including allergy.[15]

Debate over the merit of various allergy tests has been prominent in the literature in recent years. One method which has been the subject of considerable discussion is the cytotoxic test for non-IgE-mediated food allergies. This test is based on the theory that addition of an allergen to whole blood *in vitro* will cause death and disintegration of white blood cells. A study by Phil Lieberman and colleagues, Sections of Allergy-Immunology, Departments of Medicine and Pediatrics, University of Tennessee College of Medicine, Memphis, found the cytotoxic test unreliable in the diagnosis of food allergies.[16]

Since most people with allergies are sensitive to more than one allergen, more than one diagnostic test may be necessary. Ali and colleagues recommend a two-step approach to *in vitro* diagnosis of allergies. First, patients with suspected allergies should be tested with a limited group of potential allergens to identify those individuals with IgE-mediated allergies. Second, a comprehensive group of relevant regional allergens should be used to test patients with IgE-mediated allergies.[12]

**Treatment**

Once the cause of the allergy is identified, the best treatment is avoidance of the allergen. This is easily accomplished for cases of such allergens as cat or dog dander, drugs, and foods. According to Sami L. Bahna and Clifton T. Furukawa, Section of Allergy and Immunology, Department of Pediatrics, Louisiana State

University School of Medicine, New Orleans, and University of Washington School of Medicine, Seattle, dietary elimination is the most effective, least expensive, and safest means of treating food allergy. However, its success depends on proper identification of the offending allergen, degree of patient compliance, and proper labeling of food contents by the manufacturer.[17] Persons with adverse reactions to food may face difficulties in eating restaurant food, especially those with adverse reactions to food additives that are almost impossible for the diner to detect. These adverse reactions may or may not be based on IgE-mediated allergy.

Incidentally, adverse reaction to food additives was first reported in a 1959 *Annals of Allergy* case study by allergist Stephen D. Lockey, Lancaster, Pennsylvania.[18] Monosodium glutamate (MSG), which is frequently used in Chinese cooking, has been reported by David H. Allen and Gary J. Baker, Department of Thoracic Medicine, Royal North Shore Hospital, St. Leonards, Australia, to provoke attacks in patients with asthma.[19] MSG produces a toxicity reaction rather than true allergy. It is of course the culprit in Chinese restaurant syndrome otherwise known as Kwok's disease.[20,21]

Although the treatment of choice for allergy is avoiding the suspected allergen, in some cases where this is not possible, the degree of exposure can be diminished. For example, a study of 20 children with house dust allergy by Andrew B. Murray and Alexander C. Ferguson, Division of Allergy, Children's Hospital, Vancouver, British Columbia, Canada, found significant differences between groups of children whose bedrooms were kept dust-free and those whose bedrooms were not. A dust-free bedroom diminished bronchial irritation, and the authors considered it an effective means of decreasing asthma symptoms in children with house dust or house dust mite allergies.[22] Jens Korsgaard, Institute of Hygiene, University of Aarhus, and the Chest Clinic, Aarhus Municipal Hospital, Denmark, found that lowering the indoor humidity can control the concentration of house dust mites.[23]

I've discussed the adverse effects of indoor pollution on human health in the past.[24] In fact, one indoor pollutant mentioned in that essay was smoke. Since then, new evidence indicates that certain proteins present in tobacco smoke may cause allergic reactions. A recent abstract by Tova Francus and colleagues, Departments of Medicine and Pathology, Cornell University Medical College, New York, reported that one-third of normal humans exhibit immediate cutaneous, or skin hypersensitivity to tobacco glycoprotein.[25]

When the allergen cannot be avoided entirely, drugs may be necessary to control allergy symptoms. For many people, a combination of environmental control and drug therapy is necessary to achieve relief of their symptoms. And this frequently involves a compromise between the beneficial effects of the drug and undesirable side effects. According to Martin D. Valentine, Johns Hopkins University School of Medicine, Baltimore, the goal of drug therapy is to allow the patient to function normally, since complete elimination of symptoms may not be possible.[26]

Drugs for allergies generally function by acting at various sites in the sequence of the allergic reaction. For example, antihistamines block the effects of histamine, a chemical mediator of the allergic reaction. These drugs are the most popular for treating allergic rhinitis, and work well in controlling the itching and swelling associated with allergy. They are less effective in easing the breathing difficulties that occur with constriction of the bronchioles of the lungs during an asthma attack. However, William W. Douglas, Department of Pharmacology,

Yale University School of Medicine, New Haven, indicated that in therapeutic doses, all commercially available antihistamines produce side effects.[27] The most troublesome side effect is sedation or drowsiness that can interfere with daily activity to such a degree that an accident may occur while working or driving a car. As C.B.M. Tester-Dalderup, Workers Compensation Board, Edmonton, Alberta, Canada, pointed out, the sedative effect of antihistamines is marked and common, occurring in 25 to 60 percent of people taking the medication.[28]

In newer antihistamines, such as terfenadine, Tester-Dalderup, who is also advisor to the Netherlands Committee for Evaluation of Medicines, reported that the sedative effect is less pronounced.[28] In fact, a study by M.L. Brandon and M. Weiner, Allergy Medical Group of San Diego, Inc., California, found sedation in a terfenadine-treated group similar to the placebo-treated group.[29] Despite these findings, A.N. Nicholson, Royal Air Force Institute of Aviation Medicine, Farnborough, Hampshire, England, noted that the sedative effects can never be excluded in advance, and each patient must be treated on an individual basis.[30] Terfenadine is as effective as the older antihistamines in treating symptoms of seasonal allergic rhinitis.

While antihistamines interfere with a major mediator of the immediate hypersensitivity reaction, other mediators, such as prostaglandins and leukotrienes, are unaffected. Mark Ballow, Department of Pediatrics, University of Connecticut Health Center, Farmington, noted that cromolyn, a recent addition to the list of drugs used for treating allergies, acts by inhibiting the release of mediators and is most effective by local administration in treating asthma and allergic rhinitis.[31] Carlo Zanussi, Second Medical Clinic, Milan University, Italy, indicated that short-term high-dose therapy with cromolyn administered orally may also be effective in treating food allergies.[32] A 1978 paper by Paul D. Buisseret, then of the Department of Medicine, Guy's Hospital Medical School, London, and colleagues suggested that prostaglandin-synthesis inhibitors, such as non-steroidal anti-inflammatory drugs, may benefit some patients with food intolerance.[33]

Another class of drugs used in treating allergies is the corticosteroids. These are anti-inflammatory agents that also have immunosuppressive effects. Corticosteroids can be applied to the skin in cases of allergic dermatitis; inhaled for asthma, the pulmonary expression of allergy; or taken orally for allergic dermatitis and asthma. However, Lieberman and W.W. Taylor, Section of Allergy-Immunology, University of Tennessee College of Medicine, noted that corticosteroid therapy is not without risk of serious side effects, and before they are used for treating asthma, other forms of therapy should be tried.[34] The most common untoward effects of the corticosteroids are related weight gain and fluid retention. Kenneth P. Mathews, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, indicated that side effects are related to the dose, route of administration, and duration of therapy. And their use for short periods, especially during the pollen season, can, in fact, be beneficial.[35]

Newer corticosteroids, such as beclomethasone diproprionate dispensed as a nasal spray, are even more effective in controlling symptoms and are without major adverse effects. A 12-week study by Peter Small and colleagues, Departments of Medicine and Otolaryngology, Jewish General Hospital, McGill University, Montreal, Canada, compared the effects of beclomethasone diproprionate with a placebo in patients with year-round rhinitis. They found no difference between the treated and con-

trol group in incidence of side effects. And 63 percent of the beclomethasone diproprionate-treated patients achieved total or significant control of nasal symptoms.[36]

Sympathomimetic preparations are also used to control allergy symptoms. These drugs, frequently used as aerosol sprays, constrict the nasal mucosa and when administered to the lung help relieve obstruction. However, in two frequently cited papers, Frank E. Speizer and colleagues, then of the Medical Research Council's Statistical Research Unit, and University College Hospital Medical School, London, reported an association between increased deaths from asthma in Great Britain and excessive use of pressurized spray containers of isoproterenol.[37,38] Isoproterenol is one of the sympathomimetic preparations. In a *Citation Classic* commentary, Speizer, now at the Department of Medicine, Harvard Medical School, Boston, noted, "Because of these results, the Committee on Safety and Drugs, in 1967,...issued a warning to all physicians in Great Britain on the potential hazards of pressurized aerosol sympathomimetic preparations."[39]

When environmental control and drug therapy fail, immunotherapy is often beneficial for some allergies. Immunotherapy, or allergy shots, consists of injections of gradually increasing amounts of allergen in an attempt to reduce the patient's sensitivity. This method obviously depends on accurate identification of the offending allergen and works best in cases of airborne allergens and insect venom. Howard Melam, Department of Medicine, Northwestern University Medical School, Chicago, Illinois, indicated that allergy shots are not recommended for allergy to food.[40] Recent research by J. L. Ohman and colleagues, Allergy Laboratory, Veterans Administration Outpatient Clinic and Department of Medicine, Tufts University School of Medicine, Boston, suggests immunotherapy may be useful in treating selected asthmatics who are allergic to domestic cats.[41] Immunotherapy was first used by L. Noon, at the Department of Therapeutic Inoculation, St. Mary's Hospital, London, who in 1911 treated pollen-sensitive patients with injections of extracts of grass pollen.[42] Only recently, however, has insight been gained into the mechanisms by which immunotherapy acts.

Immunotherapy alters the immunologic reactions that occur in allergy so there is less response on reexposure to the allergen. Philip S. Norman, Clinical Immunology Division, Good Samaritan Hospital, Baltimore, indicated that immunotherapy works by inhibiting histamine release from basophils, a type of white blood cell, and by stimulating the production of IgG to the allergen.[43] The IgG antibody may function as a blocking antibody, presumably by combining with the allergen and preventing the reaction of IgE with effector cells that produce the chemical mediators of the allergic reaction.

An earlier study by Norman and colleagues compared immunotherapy and placebo effects in treating patients with ragweed allergy during the pollen season. They found significant differences between the two groups, and concluded that immunotherapy is effective in modifying symptoms.[44] Immunotherapy rarely cures allergy, but significant improvement in symptoms may be achieved. However, as Roy Patterson and colleagues, Department of Medicine, Northwestern University Medical School, Chicago, pointed out, to achieve beneficial effects immunotherapy generally takes six months to one year, and maximal benefit may require as long as three years of therapy.[45]

A new type of immunotherapy uses allergen modified by polymerization, or the binding together of two or more molecules. This method reduces the risk of

anaphylactic reaction to the allergen by slowing its absorption into the body. A clinical trial of this modified extract carried out by Leslie C. Grammer and colleagues, Section of Allergy-Immunology, also at Northwestern University, found polymerized grass allergen to be safe and effective in reducing symptoms.[46]

When traditional methods of allergy treatment fail to provide adequate relief, allergy sufferers may turn to nontraditional medical practices. A study by Judith Moore and colleagues, Southampton University and the Centre for the Study of Alternative Therapies, Southampton, England, found the majority of people seeking nontraditional medical treatment first tried conventional medicine.[47] Among physicians who treat allergies in a nontraditional way are the clinical ecologists. According to Iris R. Bell, Langley Porter Psychiatric Institute, University of California, San Francisco, School of Medicine, clinical ecology differs from traditional allergy in that it treats allergy-like symptoms that may or may not be IgE-mediated. Clinical ecology draws from toxicology as well as immunology.[48]

"Clinical ecologists," according to Metcalfe, "do not generally treat patients with standard allergies. In general, they are not looking at asthmatics, rhinitis, and food allergies that cause hives. Clinical ecologists tend to see patients who go to traditional physicians and don't get their problems treated in what they believe to be a successful way. Often these people may not have allergies. Their complaints involve headaches, arthralgias, abdominal bloating, tension, and fatigue. There are a lot of diseases in this differential diagnosis. Somewhere along the line these people become convinced that it's due to something in their environment. The clinical ecologists have focused on this group of individuals."[49] Many traditional allergists would not consider these as true allergy.

Like traditional allergists, clinical ecologists generally emphasize identification and elimination of the offending substance. However, the diseases treated and methods clinical ecologists use to identify and treat allergy-like symptoms are sometimes questioned by traditional allergists due to lack of controlled studies. One of their most controversial methods is provocation-neutralization testing. With this technique, allergies are diagnosed by assessing the ability of a substance to produce symptoms rather than just induce a wheal as in skin testing. Carlton H. Lee, St. Joseph, Missouri, and colleagues describe the test as consisting of a series of dilutions of potential allergen placed under the tongue or skin.[50] Only one dilution of a single substance is used at a time. Clinical ecologists claim that this method determines which substance produces symptoms, and the proper dilution of that substance for neutralizing the symptoms. Lee and colleagues note that certain dilutions of the allergen provoke symptoms while other dilutions relieve mild versions of symptoms.[50] Treatment may involve long-term therapy with neutralizing dilutions, although some patients experience immediate relief of symptoms. Food and inhalant allergies can be tested and treated with this method.

Another therapy espoused by clinical ecologists is the rotation diet described by allergist Theron G. Randolph and Ralph W. Moss in their book, *An Alternative Approach to Allergies.*[51] The rotation diet involves eating the offending foods only once every four to five days or eliminating them completely for three to six months. According to Bell, the principle of rotation is that tolerated foods will not be eaten too frequently and thus, new sensitivities will be avoided. As tolerance for offending foods re-

turns, the foods may be worked into a rotating schedule of once every four to five days without causing a sensitivity reaction.[52] (p. 48)

Many clinical ecology patients, in order to avoid the causes of their allergies, particularly chemical allergies, are instructed to dramatically change their living and work environments. According to clinical ecologist William J. Rea, Environmental Health Center, Dallas, avoiding the cause of the symptoms results in significant improvement in the patient's health.[53]

Many patients treated by clinical ecologists organize their life around their illness. Some live in an environment virtually free of the synthetic materials to which they are deemed allergic. In discussing the medical subculture of clinical ecology, Carroll M. Brodsky, Department of Psychiatry, University of California, San Francisco, School of Medicine, pointed out that traditional medicine has not adequately dealt with these problem patients.[54] Brodsky clearly raises an important issue.

In some cultures allergies are treated with a mixture of western and traditional medicine. For example, Douglas E. Johnstone and Joseph E. Ghory, Departments of Pediatrics, School of Medicine and Dentistry, University of Rochester, New York, and University of Cincinnati, Ohio, reported that asthmatic children at the allergy clinic of the Children's Hospital, Shanghai, are given bronchodilators and treated with herbal medicine and acupuncture.[55] An illustration of the efficacy of acupuncture is found in a study of asthmatic patients treated with acupuncture and isoproterenol by Donald P. Tashkin and colleagues, UCLA Acupuncture Project and Departments of Medicine, Anesthesiology, Pediatrics, Psychology, and Epidemiology, UCLA Schools of Medicine and Public Health. They found that acupuncture partially reverses the symptoms of experimentally induced bronchospasm.[56]

No matter how allergies are handled, the fact that the tendency is inherited indicates that they extend far back in human history. Since allergies presumably leave no traces on skeletal remains, we can only speculate about their adaptive advantage in evolution. T.A.E. Platts-Mills, Division of Allergy and Clinical Immunology, University of Virginia, Richmond, suggested that they may have been advantageous in stimulating local immunity in an environment, such as that of early man, where parasitic worm infestation was endemic.[57]

Various medical associations specializing in the research and treatment of allergies offer information on allergy to physicians and the general public. Some of these groups are listed in Table 1. Their membership generally includes physicians concerned with the diagnosis and treatment of allergies. Many hold annual meetings and continuing education seminars. Some sponsor a journal reflecting the interests of the society's membership. For example, *Annals of Allergy*, first published in 1943, is sponsored by the American College of Allergists. The *Journal of Allergy and Clinical Immunology* is the official publication of the American Academy of Allergy and Immunology. This journal, which began publication in 1929 under the name *Journal of Allergy*, was the first devoted to the clinical aspects of allergy.

It is always possible to abuse analogies, but medicine, like the human body, has its own built-in powers of resistance to attack by foreigners. By this I mean resistance to new ideas that challenge long-established doctrines or dogma, or as it is fashionable to say these days—paradigms. Just as Pasteur encountered resistance to his ideas, as did the early immunologists, so have the pioneers in allergy research. However, there have been too many clinicians who have been

**Table 1:** A selected list of organizations providing education, information, treatment, standards, certification, and research in allergies and clinical immunology.

Académie Européenne d'Allergologie et d'Immunologie Clinique
52 Blvd. de la Cambre
B-1050 Bruxelles
Belgium

Allergy Information Association
25 Poynter Drive, Room 7
Weston, Ontario
Canada M9R 1K8

American Academy of Allergy and Immunology
611 E. Wells Street
Milwaukee, WI 53202

American Academy of Otolaryngic Allergy
1101 Vermont Avenue, NW
Suite 302
Washington, DC 20005

American Allergy Association
P.O. Box 7273
Menlo Park, CA 94026

American Association for Clinical Immunology and Allergy
P.O. Box 912, DTS
Omaha, NE 68101

American Association of Certified Allergists
800 E. Northwest Hwy., Suite 101
Mt. Prospect, IL 60056

American College of Allergists
800 E. Northwest Hwy., Suite 101
Mt. Prospect, IL 60056

American Osteopathic College of Allergy and Immunology
8044 W. Vernor
Detroit, MI 48209

Association for the Care of Asthma
P.O. Box 568
Spring Valley Rd.
Ossining, NY 10562

Asthma and Allergy Foundation of America
1302 18th Street, NW, Suite 303
Washington, DC 20036

British Society for Allergy and Clinical Immunology
Wythenshawe Hospital
Manchester, M13 9PT
England

Histamine Research Society of North America
Department of Pharmacology
Cornell University Medical College
1300 York Avenue
New York, NY 10021

International Association of Allergology and Clinical Immunology
611 E. Wells Street
Milwaukee, WI 53202

International Correspondence Society of Allergists
5811 Outlook Drive
Shawnee Mission, KS 66202

National Institute of Allergy and Infectious Diseases
National Institutes of Health, Bldg. 31
9000 Rockville Pike
Bethesda, MD 20205

Sociedad Mexicana de Alergia e Inmunología A.C.
Fuento Emperador 6
Tecamachalco, México 10, D.F.

Società Italiana di Allergologia e Immunologia Clinica
Policlinico Umberto I
Viale del Policlinico
I-00100 Roma
Italy

Société Française d'Allergologie
1 Rue du Val-de-Grâce
F-75005
Paris
France

Society for Clinical Ecology
P.O. Box 16106
Denver, CO 80216

unprepared to do the hard scientific work necessary to support their theories. It has only been in recent years, with the parallel growth in the field of immunology, that heretical notions like an allergy-behavioral connection have become an area of increasing research interest. While this essay does not primarily concern behavioral manifestations of allergy, it is relevant to point out the recent observation by James F. Jones, Department of Pediatrics, National Jewish Hospital, Denver, and colleagues, Departments of Pediatrics, Pathology, Medical and Molecular Biology, University of Arizona College of Medicine, Tucson, that certain forms of depression may in fact be the consequence of the Epstein-Barr virus, now known to be the culprit in mononucleosis.[58] Another study of chronic Epstein-Barr virus infection by Steven E. Straus,

NIH, and colleagues, however, attributes the depression to the chronicity of the illness,[59] rather than directly to the virus. The fact that Jones and colleagues found that a large number of these people have IgE-mediated allergic disease makes this all the more intriguing.[60]

The third part of this essay will discuss in detail what we know about the behavioral manifestations of allergy and the need for additional research in such areas as psychoimmunology. It will also include a discussion of core research papers dealing with allergies and their behavioral consequences.

* * * * *

*My thanks to Cecelia Fiscus and Linda LaRue for their help in the preparation of this essay. Thanks also to the many reviewers, most of them cited above, who helped increase the accuracy of this essay.*



## REFERENCES


1. **Garfield E.** Allergies are nothing to sneeze at. Part 1. Epidemiology and etiology. *Current Contents* (13):3-15, 1 April 1985.
2. **Pécoud A, Bonstein H S & Frei P C.** Value of the case history in the diagnosis of allergic state and the detection of allergens. *Clin. Allergy* 13:141-7, 1983.
3. **Atkins F M & Metcalfe D D.** The diagnosis and treatment of food allergy. *Annu. Rev. Nutr.* 4:233-55, 1984.
4. **Nelson H S.** Diagnostic procedures in allergy. I. Allergy skin testing. *Ann. Allergy* 51:411-8, 1983.
5. **Ishizaka K & Ishizaka T.** Identification of γE-antibodies as a carrier of reaginic activity. *J. Immunol.* 99:1187-98, 1967.
6. **Wide L, Bennich H & Johansson S G O.** Diagnosis of allergy by an in-vitro test for allergen antibodies. *Lancet* 2:1105-7, 1967.
7. **Wide L.** Citation Classic. Commentary on *Lancet* 2:1105-7, 1967. *Current Contents/Life Sciences* 28(3):19, 21 January 1985.
8. **Booth B H.** Diagnosis of immediate hypersensitivity. (Patterson R, ed.) *Allergic diseases.* Philadelphia: Lippincott, 1980. p. 76-99.
9. **Bock S A.** Food sensitivity. *Amer. J. Dis. Child.* 134:973-82, 1980.
10. **Engvall E & Perlmann P.** Enzyme-linked immunosorbent assay, ELISA. III. Quantitation of specific antibodies by enzyme-labeled anti-immunoglobulin in antigen-coated tubes. *J. Immunol.* 109:129-35, 1972.
11. **Subba Rao P V, McCartney-Francis N L & Metcalfe D D.** An avidin-biotin microELISA for rapid measurement of total and allergen-specific human IgE. *J. Immunol. Method.* 57:71-85, 1983.
12. **Ali M, Ramanarayanan M P & Prasad K.** Diagnosis and management of allergic disorders: the future is here. *Diagn. Med.* 7(4):48-59, 1984.
13. **Grieco M H.** Controversial practices in allergy. *JAMA—J. Am. Med. Assn.* 247:3106-11, 1982.
14. **Sampson H A & Albergo R.** Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J. Allerg. Clin. Immunol.* 74:26-33, 1984.
15. **Kohler P F, Buckley R H & Bloch K J.** Implications of "certification in diagnostic laboratory immunology" for the training and practice in allergy-immunology. *J. Allerg. Clin. Immunol.* 72:121-2, 1983.
16. **Lieberman P, Crawford L, Bjelland J, Connell B & Rice M.** Controlled study of the cytotoxic food test. *JAMA—J. Am. Med. Assn.* 231:728-30, 1975.
17. **Bahna S L & Furukawa C T.** Food allergy: diagnosis and treatment. *Ann. Allergy* 51:574-80, 1983.
18. **Lockey S D.** Allergic reactions due to FD&C Yellow no. 5 Tartrazine, an aniline dye used as a coloring and identifying agent in various steroids. *Ann. Allergy* 17:719-21, 1959.
19. **Allen D H & Baker G J.** Letter to editor. (Asthma and MSG.) *Med. J. Aust.* 2:576, 1981.
20. **Garfield E.** What's in a name? The eponymic route to immortality. *Essays of an information scientist.* Philadelphia: ISI Press, 1984. Vol. 6. p. 384-95.
21. **Kwok R H M.** Letter to editor. (Chinese-restaurant syndrome.) *N. Engl. J. Med.* 278:796, 1968.
22. **Murray A B & Ferguson A C.** Dust-free bedrooms in the treatment of asthmatic children with house dust or house dust mite allergy: a controlled trial. *Pediatrics* 71:418-22, 1983.
23. **Korsgaard J.** Preventive measures in house-dust allergy. *Amer. Rev. Resp. Dis.* 125:80-4, 1981.
24. **Garfield E.** Indoor pollution: why environmental protection may also be an inside job. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 66-71.
25. **Francus T, Siskind G W & Becker C G.** Tobacco glycoprotein (TGP) elicits an exclusive IgE response. (Abstract.) *Fed. Proc.* 42:712, 1983.

26. **Valentine M D.** Allergy and infectious diseases: allergy and related conditions. (Barker L R, Burton J R & Zieve P D, eds.) *Principles of ambulatory medicine.* Baltimore: Williams & Wilkins, 1982. p. 173-89.
27. **Douglas W W.** Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. (Goodman L S & Gilman A.) *The pharmacological basis of therapeutics.* New York: Macmillan, 1980. p. 609-46.
28. **Tester-Dalderup C B M.** Antihistamines. *Side Effect. Drug. Annu.* 8:165-9, 1984.
29. **Brandon M L & Welner M.** Clinical studies of terfenadine in seasonal allergic rhinitis. *Arzneim.-Forsch.-Drug Res.* 32:1204-5, 1982.
30. **Nicholson A N.** Antihistamines and sedation. *Lancet* 2:211-2, 1983.
31. **Ballow M.** Allergic rhinitis and conjunctivitis. *Postgrad. Med.* 76:197-206, 1984.
32. **Zanussi C.** Food allergy treatment. *Clin. Immunol. Allergy* 2:221-40, 1982.
33. **Buisseret P D, Heinzelmann D I, Youlten L J F & Lessof M H.** Prostaglandin-synthesis inhibitors in prophylaxis of food intolerance. *Lancet* 1:906-8, 1978.
34. **Lieberman P & Taylor W W.** Corticosteroids in the treatment of allergic diseases. (Patterson R, ed.) *Allergic diseases.* Philadelphia: Lippincott, 1980. p. 654-70.
35. **Mathews K P.** Respiratory atopic disease. *JAMA—J. Am. Med. Assn.* 248:2587-610, 1982.
36. **Small P, Black M & Frenkiel S.** Effects of treatment with beclomethasone dipropionate in subpopulations of perennial rhinitis patients. *J. Allerg. Clin. Immunol.* 70:178-82, 1982.
37. **Speizer F E, Doll R & Heaf P.** Observations on recent increase in mortality from asthma. *Brit. Med. J.* 1:335-9, 1968.
38. **Speizer F E, Doll R, Heaf P & Strang L B.** Investigation into use of drugs preceding death from asthma. *Brit. Med. J.* 1:339-43, 1968.
39. **Speizer F E.** Citation Classic. Commentary on *Brit. Med. J.* 1:335-9, 1968. *Current Contents/Life Sciences* 28(14):17, 8 April 1985.
40. **Melam H.** Principles of immunologic management of allergic diseases due to extrinsic antigens. (Patterson R, ed.) *Allergic diseases.* Philadelphia: Lippincott, 1980. p. 326-39.
41. **Ohman J L, Findlay S R & Leitermann K M.** Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of in vivo and in vitro responses. *J. Allerg. Clin. Immunol.* 74:230-9, 1984.
42. **Noon L.** Prophylactic inoculation against hay fever. *Lancet* 1:1572-3, 1911.
43. **Norman P S.** An overview of immunotherapy: implications for the future. *J. Allerg. Clin. Immunol.* 65:87-96, 1980.
44. **Norman P S, Winkenwerder W L & Lichtenstein L M.** Trials of alum-precipitated pollen extracts in the treatment of hay fever. *J. Allerg. Clin. Immunol.* 50:31-44, 1972.
45. **Patterson R, Norman P & Van Metre T.** Immunotherapy-immunomodulation. *JAMA—J. Am. Med. Assn.* 26:2759-72, 1982.
46. **Grammer L C, Shaughnessy M A, Suszko I M, Shaughnessy J J & Patterson R.** A double-blind histamine placebo-controlled trial of polymerized whole grass for immunotherapy of grass allergy. *J. Allerg. Clin. Immunol.* 72:448-53, 1983.
47. **Moore J, Phipps K, Marcer D & Lewith G.** Why do people seek treatment by alternative medicine? *Brit. Med. J.* 290(1):28-9, 1985.
48. **Bell I R.** Telephone communication. 26 March 1985.
49. **Metcalfe D D.** Telephone communication. 27 March 1985.
50. **Lee C H, Williams R I, Wyo C & Binkley E L.** Provocative testing and treatment for foods. *Arch. Otolaryngol.* 90:113-20, 1969.
51. **Randolph T G & Moss R W.** *An alternative approach to allergies.* New York: Bantam Books, 1980. 311 p.
52. **Bell I R.** *Clinical ecology. A new medical approach to environmental illness.* Bolinas, CA: Common Knowledge Press, 1982. 79 p.
53. **Rea W J.** Telephone communication. 28 March 1985.
54. **Brodsky C M.** 'Allergic to everything': a medical subculture. *Psychosomatics* 24:731-42, 1983.
55. **Johnstone D E & Ghory J E.** Two pediatric allergists' sojourn in the People's Republic of China. *Ann. Allergy* 42:5-10, 1979.
56. **Tashkin D P, Bresler D E, Kroening R J, Kerschner H, Katz R L & Coulson A.** Comparison of real and simulated acupuncture and isoproterenol in methacholine-induced asthma. *Ann. Allergy* 39:379-87, 1977.
57. **Platts-Mills T A E.** The biological role of allergy. (Lessof M H, ed.) *Allergy: immunological and clinical aspects.* New York: Wiley, 1984. p. 1-43.
58. **Jones J F, Ray C G, Minnich L L, Hicks M J, Kibler R & Lucas D O.** Evidence for active Epstein-Barr virus infection in patients with persistent unexplained illness: elevated anti-early antigen antibodies. *Ann. Intern. Med.* 102(1):1-7, 1985.
59. **Straus S E, Tosato G, Armstrong G, Lawley T, Preble O T, Henle W, Davey R, Pearson G, Epstein J, Brus I & Blaese R M.** Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. *Ann. Intern. Med.* 102(1):7-16, 1985.
60. **Jones J F.** Telephone communication. 26 March 1985.