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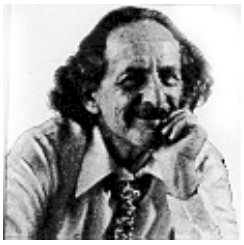

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Allergies Are Nothing to Sneeze At. Part 3. Behavioral Manifestations

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We recently discussed the widespread occurrence of allergies and the various means of diagnosing and treating them.[1] Although allergy symptoms are generally associated with physical problems, research shows that behavioral problems such as hyperactivity in children, depression, and possibly even schizophrenia may also be associated with allergy. Part three will focus on behavioral aspects of adverse reactions and allergies to various aspects of our environment. Allergies are abnormal reactions to ordinarily harmless substances and are generally mediated by IgE antibodies. Antibodies are a class of proteins known as immunoglobulins and can be an indication of allergy. IgE antibodies are associated with immediate hypersensitivity allergic reactions. Unlike allergies, adverse reactions may or may not be mediated by the immune system.

There are several possible connections between allergy and behavioral problems. Psychologist David S. King, Langley Porter Psychiatric Institute, San Francisco, California, notes that allergy symptoms can be produced or aggravated by psychological factors. Another connection is the detrimental effect of the allergy problem on the psychological state of the allergic individual. And allergy exposure may be directly responsible for both psychological and somatic symptoms.[2]

In a double-blind study, King examined the psychological changes in 30 allergy patients exposed to various allergens or to a placebo. He found that changes in behavior can be produced in selected individuals by exposure to an allergen but not to the placebo. This finding lends support to the reports that allergies may cause some behavioral and psychiatric problems.[2] A review of pseudo-allergic reactions to food by David J. Pearson and Keith J.B. Rix, Departments of Medicine and Psychiatry, University of Manchester and University of Leeds, UK, found evidence for psychological and social problems secondary to the well-recognized physical effects of allergy.[3] However, they found no published evidence to support claims that multiple nonallergic symptoms or psychological disorders are commonly a direct result of allergy.

Pseudo-allergic reactions are disorders of psychological origin with symptoms that mimic those of an allergic disease but are not mediated by the immune system. True food allergies are hypersensitivity reactions mediated by the immune system. Pearson notes that immunologically mediated food allergy is less common in adults than other forms of allergy. In fact, the most common reason for intolerance of certain foods is psychological rather than immunologic.[4]

Emotional Factors in Asthma

One of the major forms of allergy is asthma. Asthma is a breathing disorder in which a recurrent, although reversible, bronchoconstriction causes obstruction to airflow in the lungs. Patients with asthma are usually symptom-free between periodic acute exacerbations of their illness. Emotional factors can precipitate an asthma attack in some pa-

tients. For example, Douglas J. Horton and colleagues, Department of Medicine, National Jewish Hospital and Research Center, and Departments of Medicine and Psychiatry, University of Colorado School of Medicine, Denver, examined the relationship between emotional reactions to a neutral substance presented as an allergen and changes in the airway. They found that an emotional response to the neutral stimulus, as indicated by physiological measures, led to airway obstruction in some asthmatics.[5] The fact that much research on the behavioral aspects of asthma has been done at the National Jewish Hospital and Research Center is directly attributable to Richard S. Farr. As past chairman of the Department of Medicine, he brought together a group of researchers specifically to study this problem.

Farr suggests that the presence of emotional factors in asthma and the associated anger may be a result of the asthma rather than a cause of it.[6] This is illustrated by the case-history report by pediatrician Jerome M. Buckley, University of Colorado Medical Center and National Jewish Hospital-National Asthma Center, which demonstrates that stabilizing the asthma condition affects the patient's psychological outlook. Before the asthma was brought under control, psychological tests showed that the patient felt alone and alienated from his family and friends. Once the asthma was under control, the patient's test picture showed a greatly improved outlook.[7] In fact, Mary Norrish and colleagues, Departments of Pediatrics, Neonatal Medicine and Psychological Medicine, Hammersmith Hospital, London, reported that emotional or conduct disorders are more frequent in asthmatic children who are poorly controlled by medicine than among other asthmatic children.[8]

Allergist John P. McGovern, University of Texas School of Biomedical Sciences, Houston, and psychiatrist James A. Knight, Tulane University School of Medicine, New Orleans, noted that, as early as Hippocrates, asthmatics were advised to avoid strong emotions such as anger.[9] McGovern cites a 1922 paper by Edoardo Weiss, Psychiatric Hospital, Trieste, Italy. He presumably used psychoanalysis to treat asthma. In the paper Weiss suggests that asthma attacks represent intense dependency needs.[10] Another theory, termed the psychogenic approach by Nelson F. Jones, University of Denver, and colleagues, National Jewish Hospital and Research Center, suggests that the physical illness produces a unique set of personality traits.[11] To better define these traits, Jones and colleagues administered the Minnesota Multiphasic Personality Inventory to 155 asthmatic patients. However, they found the pattern that emerged could better be explained by age, sex, and duration of the illness rather than by the illness itself.[11]

In a 1983 review of recent literature, psychologists Thomas L. Creer and Harry Kotses, Ohio University, Athens, note a trend away from examining global personality differences between asthmatic and nonasthmatic children. The differences are a reflection of the asthmatic condition rather than a prerequisite for it.[12]

Psychiatrists Suhayl J. Nasr and Robert W. Atkins, University of Rochester Medical Center, New York, treated two asthmatic patients with lithium for relief of manic-depressive illness. They found that not only did the psychiatric problems improve but also the asthma improved with this drug. Both patients were free of asthma attacks during lithium therapy. Nasr and Atkins suggest that this implies an interaction among lithium, cyclic nucleotides, and prostaglandin, one of the mediators of the immediate hypersensitivity reaction.[13]

Allergy and Depression

We've previously discussed the various causes of depression; however, we did not mention allergy as a possible cause in those essays.[14] In a study of the

relationship between allergy and depression, Paul Matussek and colleagues, Research Institute for Psychopathology and Psychotherapy, Max Planck Society for the Promotion of Science, Munich, examined 172 depressed patients and a control group of 42 nondepressed individuals.[15] They found that the frequency of allergy did not differ significantly between the depressed and control groups. However, when the entire group of depressed patients was subdivided into various diagnostic categories of depression, the highest frequency of allergy was found in monopolar endogenous depressive females. A significantly lower incidence of allergy was found in bipolar endogenously depressed women than in the control group. Bipolar depression includes episodes of mania, whereas the monopolar condition involves only depression. Although no differences were found for men, this may be a reflection of the small sample of men in the study rather than of a significant sex difference.

The connection between allergy and depression and the reason that lithium therapy improves symptoms for both may lie in the differences in platelet histamine accumulation in depressed and nondepressed patients. There is evidence that accumulation of histamine, another mediator of the immediate hypersensitivity reaction, was significantly decreased in the platelets of depressed females compared to a normal control group. In a subsequent study that included males, Keith Wood and colleagues, Medical Research Council, West Park Hospital, Surrey, UK, found that depressed patients had the lowest histamine accumulation rate and the highest platelet count while the controls had the lowest platelet count, and the lithium-treated patients had an intermediate accumulation rate and platelet count.[16] However, Michael Kaliner, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland, indicated that the assay methods in this study are old, less accurate, and less sensitive than current assays.[17]

A. Arthur Sugerman, Carrier Foundation, Belle Mead, and colleagues, Princeton Allergy Associates and Immunodiagnostic Research Foundation, New Jersey, studied IgE levels in depressed patients, alcoholics, and schizophrenics.[18] They found a high level of circulating IgE, or reagenic antibody, in these patients. In the schizophrenic group, 90 percent demonstrated a positive reaction to milk. I discussed the various biological and psychological theories of schizophrenia previously.[19]

Food Allergy and Schizophrenia

The idea that allergy to milk and cereal grains plays a role in schizophrenia was supported by the 1969 work of F.C. Dohan, then at the William Pepper Laboratory of Clinical Medicine, Hospital of the University of Pennsylvania, Philadelphia, and colleagues. Schizophrenics in a locked ward were maintained on a milk- and cereal-free diet or on a high-cereal diet. Those on a milk- and cereal-free diet were released to an open ward more rapidly than patients on a high-cereal diet.[20] In a 1973 study, Dohan and J.C. Grasberger, Veterans Administration Hospital, Coatesville, Pennsylvania, found that schizophrenics on a milk- and cereal-free diet were released from the hospital twice as fast as those given the regular hospital diet.[21]

Much more recently, Dohan and colleagues further tested this hypothesis by comparing the incidence of schizophrenia in a New Guinea population that consumes little or no grain or milk with one that consumes grain but no milk. They found that schizophrenia is infrequent in tribal populations where grains and milk are rare and more frequent in similar populations that consume grains but not milk.[22] These researchers suggest that neuroactive peptides from grain glutens may cause schizophrenia in genetically predisposed individuals. Recently Lynn E. DeLisi, Richard J. Weber, and Candace B. Pert, Neurogenetics Section, National Institute of Mental Health, NIH, reported that 18 percent of the 69 hospitalized psychi-

atric patients presented evidence of antibodies against their own brain tissue. They did not find any conclusive evidence for the cause of these increased antibodies. The researchers indicate that this work is preliminary and that further work may provide more evidence of the exact association.[23] However, the presence of these antibodies in no way indicates that there is a causal relationship between allergies and these antibodies.

Adverse reactions to food have been blamed for various psychological and neurological symptoms, including schizophrenia, depression, and migraine. In 1982 H.G. Kinnell and colleagues, Botleys Park Hospital, Chertsey, Surrey, and the Western Infirmary, Glasgow, reported on their test of the food-allergy theory of schizophrenia.[24] They measured antibodies to wheat, milk, and other dietary proteins in schizophrenics. They found antibodies to food in only a minority of the patients. A similar study by Peter McGuffin, Institute of Psychiatry, London, and colleagues, Freeman Hospital, Newcastle upon Tyne, and St. James's University Hospital, Leeds, compared 31 schizophrenics and 30 normals. They could not find evidence that food allergy plays a role in the etiology of schizophrenia.[25] However, in a 1981 letter in *Biological Psychiatry*, Dohan indicates that McGuffin's sample sizes may have been too small to detect a significant difference between the control and schizophrenic groups.[26]

The idea that allergy to certain foods may cause behavioral changes has been speculative. This may be related to the fact that, in some cases, foods do not produce symptoms that are obviously related to an allergic reaction. However, in 1978 Ronald Finn and H. Newman Cohen, Royal Southern Hospital, Liverpool, and Department of Medicine, University of Liverpool, presented case studies that illustrate the diffuse symptoms caused by food allergies.[27] Along with other symptoms, their patients suffered from psychological problems such as migraine, depression, suicidal thoughts, and panic attacks. Finn and Cohen suggested that although some of these behavioral symptoms may be attributed to the persistence of other associated physical symptoms, some of the behavioral symptoms may be a direct consequence of the allergy. In 1984 Nancy P. Cummings and S. Allan Bock, National Jewish Hospital and Research Center, reported that they examined 10 children for the possible occurrence of food-related behavioral changes. In none was a behavioral change confirmed with double-blind food challenges.[28]

Adverse Reactions to Food and Hyperactivity

Both adverse reactions to food additives and genuine food allergies have also been linked to hyperactivity in children. Hyperactivity is a childhood behavioral disorder with symptoms that include overactivity, inattentiveness, learning and behavioral problems, and immaturity. Hyperactivity has been associated with both food allergy and adverse reaction to food. Ronald L. Trites and colleagues, Neuropsychology Laboratory, Royal Ottawa Hospital, Canada; Health Protection Branch, Health and Welfare Canada, Ottawa; and Psychology Department, Carleton University, Ottawa, found that the evidence for food allergies as a cause of hyperactivity is strongest among hyperactive children who are also learning disabled and have evidence of minimal brain dysfunction.[29]

The theory that adverse reaction to food is associated with hyperactivity is the basis of the well-known Feingold diet, developed in the 1970s by allergist Ben F. Feingold, recently deceased and formerly of the Kaiser-Permanente Medical Center, San Francisco, and used to treat hyperactive children. Feingold's diet eliminates all foods with a natural salicylate radical, which is found in such diverse foods as ice cream, apples, oranges, jams and jellies, and all synthetic colors and flavors.[30] However,

there is controversy regarding the efficacy of this diet in controlling hyperactivity in children.

Jeffrey A. Mattes and Rachel Gittelman, Long Island Jewish-Hillside Medical Center, Glen Oaks, and Department of Psychology, New York State Psychiatric Institute, New York, studied 11 hyperactive children treated with the Feingold diet.[31] When these school-age children were challenged with food coloring, they showed no behavioral change. Bernard Weiss, Environmental Health Sciences Center, University of Rochester School of Medicine and Dentistry, and colleagues challenged 22 children on the Feingold diet with food coloring.[32] They found no convincing evidence of sensitivity to the challenge. However, Weiss reviewed several studies that used the Feingold diet to control hyperactivity. He concluded that some children diagnosed as hyperactive do improve on the Feingold diet and that younger children are more responsive to the diet than older ones.[33]

Allergist Doris J. Rapp, Meyer Memorial Hospital, Buffalo, New York, studied the effects of food and food-additive challenge on 24 hyperactive children. In 1978 she found food dyes are most consistently associated with hyperactivity.[34] However, in a short review of the dietary origin of hyperactivity, Eric Taylor, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, London, concluded that there is no persuasive evidence that intolerance of food additives is a major cause of hyperactivity.[35] Additive-elimination diets require more research, and more independent evidence of the role of allergy in hyperactivity is needed to justify the use of additive-elimination diets.

In 1982 NIH convened a consensus-development conference to evaluate evidence on the efficacy of dietary control, including the Feingold diet, on childhood hyperactivity. Panel members included specialists in allergy, psychiatry and behavioral science, epidemiology, and nutrition. The conclusions, published in *JAMA*, were that the bulk of evidence does not support the dietary hypothesis.[36] However, they do not exclude the possibility that hyperactive behavior may be caused by food dyes in a few cases.

Allergy and Migraine

Another symptom associated with allergy is migraine. Jean Monro and colleagues, National Hospital for Nervous Diseases, and Department of Immunology, Middlesex Hospital Medical School, London, studied nine patients with severe migraine.[37] They found that food challenge provoked migraine and that pretreatment with oral sodium cromoglycate, a disodium salt of 1,3 bis (2 carboxychromon-5-y(oxy)-2-hydroxypropane, exerted a protective effect. Sodium cromoglycate is one of the drugs reported to be effective in treating food allergies. Oral sodium cromoglycate acts by inhibiting increased intestinal permeability to macromolecules and by blocking the release of mediators of the hypersensitivity reaction. The work by Monro and colleagues suggests that food allergy may produce migraine in sensitive patients. Their sensitivities to various foods were demonstrated by elimination, challenge, and positive skin testing.

A 1983 study of 99 children with migraine examined the role allergy plays in this problem. J. Egger and colleagues, Departments of Neurology and Immunology, Hospital for Sick Children, and Institute of Child Health, London, found that most children with severe migraine recover when allergens are eliminated from their diet and that the migraine symptoms can be provoked by a wide range of foods.[38] This range of foods, they suggest, precludes a metabolic disorder and supports allergy as the source of the symptoms. However, IgE antibody levels were not increased in these patients. Increased IgE levels are characteristic of immediate hypersensitivity reactions. A study by D. Ratner, Department of Emergency Medicine, Central Emek Hospital, Afula, Israel, and

colleagues found increased levels of only IgM antibodies, which are not generally associated with immediate hypersensitivity reactions in migraine patients with milk allergy and lactase deficiency.[39] The researchers suggest that these patients have an IgM-mediated milk allergy.

Food sensitivity has also been suggested as a contributing cause of epilepsy. John W. Crayton and colleagues, Department of Psychiatry, University of Chicago, and Forest Hospital, Des Plaines, Illinois, reported a case of epilepsy traced to ingestion of beef.[40] The food-epilepsy relationship was confirmed by a carefully controlled double-blind study. The researchers found that almost two hours after ingesting a capsule containing six grams of beef, the patient had the first of six grand mal seizures. Ingestion of six grams of chicken, to which the patient had no history of allergy, produced no symptoms. The patient was put on a diet that excluded beef and had only one seizure in the next six months. In the six months prior to the exclusion diet, she had had 31 seizures. Crayton and colleagues suggest that food allergy should be considered in some epileptic patients with a history of other allergies.[40] However, Pearson and colleagues studied 23 allergy patients and were unable to find evidence that food allergy results in symptoms other than those generally associated with allergy.[41]

Psychoneuroimmunology

In 1980 psychoneuroimmunologist Robert Ader, Department of Psychiatry, University of Rochester School of Medicine and Dentistry, discussed the link between the central nervous system and the immune processes.[42] This is well illustrated by Horton's research mentioned earlier.[5] In fact, George F. Solomon, Department of Psychiatry, University of California, San Francisco, and immunologist Alfred A. Amkraut, Alza Research, Palo Alto, California, reported that asthmatic patients generally have elevated IgE levels. Animal experiments show that IgE levels can be increased by stress.[43]

Psychoneuroimmunology is a new and emerging specialty that examines the interaction of the mind, endocrine system, and immunity. The question of how these three systems interact and what can be done to predict and control these interactions remain to be answered. More will be said about this new research specialty in a future essay.

Research Fronts on the Behavioral Aspects of Allergy

Analysis of the literature on the behavioral aspects of allergy reflects the trends and directions of that research. Each year ISI® uses the combined *Science Citation Index®* (*SCI®*)/*Social Sciences Citation Index®* (*SSCI®*) to create a frequency-ranked file of papers cited that year. From this file approximately the top 1 percent is used to identify a much larger list of papers that are cited together. This list of co-cited pairs is used to generate about 10,000 clusters of two or more core papers. Using a single-link clustering algorithm, these groups of papers can be enlarged by adjusting thresholds for co-citation strength and citation frequency. Larger second-level clusters can be created by clustering the clusters identified at the first level. About 1,500 second-level clusters are obtained from the initial 10,000 first-level research fronts.

There are two 1984 research fronts dealing directly with the behavioral aspect of allergies. One is research front #84-5713, "Relationship of migraine to food allergy." There are two core papers for this research front, one by Monro and colleagues[37] and the other by Egger and colleagues.[38] Research front #84-6021, "Effects of diet and food allergy on behavior," has five core publications. They are the papers by King,[2] Pearson,[41] and Finn and Cohen,[27] as well as a paper by R. F. Harrell, Old Dominion University, Norfolk, Virginia, and colleagues describing the use of nutritional supplements in treating mental retardation[44] and Feingold's book

describing his diet for hyperactive children.[30] Only a dozen papers on the behavioral aspects of allergy were published in 1983 and 1984. When the two research fronts are combined we obtain the larger higher-level cluster "Relation of food allergy to migraines and behavior."

Journals covered in the *SCI* and *SSCI* that include articles on the behavioral aspects of allergy are in fact mainly journals dealing with psychiatry and behavioral medicine. These are listed in Table 1 with their associated 1983 impact factors and the year the journal began publication. Impact indicates how often, on the average, articles published by a certain journal in a given two-year period were cited during a particular year. The impact factors given in Table 1 were derived by dividing the number of 1983 citations to 1981 and 1982 articles by the number of articles published in 1981 and 1982. But impact can be calculated using different baselines.

Table 1: Selected list of periodicals covered by ISI® that report on behavioral aspects of allergy. A = name of journal. B = 1983 impact factor. C = year journal started.

A	B	C
American Journal of Clinical Nutrition	2.64	1952
American Journal of Psychiatry	3.21	1844
Archives of Disease in Childhood	1.62	1926
Biological Psychiatry	2.86	1969
British Journal of Psychiatry	2.39	1853
Comprehensive Psychiatry	1.04	1960
General Hospital Psychiatry	0.70	1979
Journal of Child Psychology and Psychiatry	1.69	1960
Journal of Affective Disorders	2.75	1979
Journal of Clinical Psychology	0.43	1945
Journal of Learning Disabilities	0.46	1968
Journal of Orthomolecular Psychiatry	0.25	1967
Journal of Psychosomatic Research	0.79	1956
Journal of the American Academy of Child Psychiatry	1.34	1962
Psychological Medicine	2.37	1970
Psychosomatic Medicine	2.24	1939

Summary of Behavioral Aspects of Allergy

The behavioral aspects of allergy are still controversial. While there is no hard evidence that behavioral problems are a direct result of allergy, some research does suggest a connection. However, Kaliner indicated that much of this research is anecdotal and that it is based on single case reports rather than on research involving controlled trials.[17] Asthma has an emotional component in that stress can precipitate an attack. This implies that behavior can influence the immune system to release mediators of the allergic reaction. However, in many cases of the allergy-behavior connection, the cause and effect relationship is not entirely clear. For example, in part two of this essay we mentioned the recent work of James F. Jones, Department of Pediatrics, National Jewish Hospital, and colleagues, Departments of Pediatrics, Pathology, and Medical and Molecular Biology, University of Arizona College of Medicine, Tucson. They reported an association between depression, a high frequency of allergy, and infection with the Epstein-Barr virus.[45] Further research will clarify the nature of the relationship between allergy and behavioral changes and will provide information on the relationship between behavior and the immune and nervous systems.

Allergy Journal Studies

As a conclusion to this three-part series, let's examine the activity and direction of allergy-research literature from another perspective. This is provided by reviewing the publications most cited by articles in core allergy journals. Table 2 shows the number of articles published in 1983 by the core allergy journals together with each journal's impact factor and the number of references cited. The most-cited articles for this study were identified by creating a mini-Citation Index for the 17,630 references cited in the 1983 editions of eight of the core allergy journals. We then ranked all cited papers by citation frequency.

Table 2: Number of 1983 items published in core allergy journals. A = name of journal. B = number of source items. C = impact factor. D = number of references cited.

A	B	C	D
Allergologia et Immunopathologia	38	0.09	*
Allergy	73	1.47	1,625
Annals of Allergy	141	0.76	3,493
Clinical Allergy	71	1.46	1,127
Contact Dermatitis	197	0.63	1,599
International Archives of Allergy and Applied Immunology	196	1.26	4,080
Journal of Allergy and Clinical Immunology	162	3.38	4,388
Journal of Asthma	50	0.18	*
Monographs in Allergy	53	2.93	*
Progress in Allergy	23	6.33	876
Revue Francaise d'Allergologie et d'Immunologie Clinique	26	0.16	442
Total	1,030		17,630

*Information unavailable

Twelve papers published in the core journals that were cited at least nine times by the core are listed in Table 3. The paper by L.M. Lichtenstein and colleagues, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, is the most-cited and most recent paper.[46] It concerns the diagnosis and treatment of insect hypersensitivity.

The 14 most-cited articles published in noncore journals (journals not primarily concerned with allergy research) are listed in Table 4. The list also includes another paper in the *New England Journal of Medicine* on insect hypersensitivity by K.J. Hunt and colleagues, Department of Medicine, Johns Hopkins University School of Medicine.[47] In comparing these two tables it becomes apparent that "core" allergy journals are primarily clinical and that the noncore journals emphasize basic research. Papers in *Lancet* such as that by L. Wide and colleagues, Department of Clinical Chemistry, University Hospital, Uppsala, Sweden,[48] and other papers in the table show the difficulty of such arbitrary classifications in "basic" clinical investigations.

Another perspective on allergy research is provided through analysis of research fronts cited by core allergy jour-

Table 3: Most-cited articles from core allergy journals. A = number of 1983 citations received, *SCI®*. B = bibliographic data.

A	B
9	**Aas K.** The diagnosis of hypersensitivity to ingested foods. *Clin. Allergy* 8:39-50, 1978.
9	**Aas K & Belin L.** Standardization of diagnostic work in allergy. *Acta Allergol.* 27:439-68, 1972.
18	**Ceska M, Eriksson R & Varga J M.** Radioimmunosorbent assay of allergens. *J. Allerg. Clin. Immunol.* 49:1-9, 1972.
12	**Chai H, Farr R S, Froehlich L A, Mathison D A, McLean J A, Rosenthal R R, Sheffer A L, Spector S L & Townley R G.** Standardization of bronchial inhalation challenge procedures. *J. Allerg. Clin. Immunol.* 56:323-7, 1975.
9	**Dolovich J, Hargreave F E, Chalmers R, Shier K J, Gauldie J & Bienenstock J.** Late cutaneous allergic responses in isolated IgE-dependent reactions. *J. Allerg. Clin. Immunol.* 52:38-46, 1973.
13	**Hannuksela M & Lahti A.** Immediate reactions to fruits and vegetables. *Contact Dermatitis* 3:79-84, 1977.
9	**Levine B B & Vaz N M.** Effect of combinations of inbred strain, antigen, and antigen dose on immune responsiveness and reagin production in the mouse. *Int. Arch. Allergy Appl. Immunol.* 39:156-71, 1970.
21	**Lichtenstein L M, Valentine M D & Sobotka A K.** Insect allergy: the state of the art. *J. Allerg. Clin. Immunol.* 64:5-12, 1979.
17	**Lowenstein H.** Quantitative immunoelectrophoretic methods as a tool for the analysis and isolation of allergens. *Prog. Allergy* 25:1-62, 1978.
9	**May C D, Lyman M, Alberto R & Cheng J.** Procedures for immunochemical study of histamine release from leukocytes with small volume of blood. *J. Allergy* 46:12-20, 1970.
10	**Moore V L, Fink J N, Barboriak J J, Ruff L L & Schlueter D P.** Immunologic events in pigeon breeders' disease. *J. Allerg. Clin. Immunol.* 53:319-28, 1974.
12	**Szentivanyi A.** The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J. Allergy* 42:203-32, 1968.

Table 4: Most-cited articles published in noncore allergy journals. A = number of 1983 citations received. B = bibliographic data.

A	B
11	**Beaven M A, Jacobsen S & Horakova Z.** Modification of the enzymatic isotopic assay of histamine and its application to measurement of histamine in tissues, serum and urine. *Clin. Chim. Acta* 37:91-103, 1972.
12	**Boyum A.** Isolation of mononuclear cells and granulocytes from human blood. Isolation of mononuclear cells by one centrifugation, and of granulocytes by combining centrifugation and sedimentation at 1 G. *Scand. J. Clin. Lab. Invest.* 21(Suppl.):77-89, 1968.
14	**Ceska M & Lundkvist U.** A new and simple radioimmunoassay method for the determination of IgE. *Immunochemistry* 9:1021-30, 1972.
13	**Hunt K J, Valentine M D, Sobotka A K, Benton A W, Amodio F J & Lichtenstein L M.** A controlled trial of immunotherapy in insect hypersensitivity. *N. Engl. J. Med.* 299:157-61, 1978.
9	**Laemmli U K.** Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* 227:680-5, 1970.
21	**Lowry O H, Rosebrough N J, Farr A L & Randall R J.** Protein measurement with the Folin phenol reagent. *J. Biol. Chem.* 193:265-75, 1951.
10	**Mancini G, Carbonara A O & Heremans J F.** Immunochemical quantification of antigens by single radial immunodiffusion. *Immunochemistry* 2:235-54, 1965.
10	**Matthew D J, Norman A P, Taylor B, Turner M W & Soothill J F.** Prevention of eczema. *Lancet* 1:321-4, 1977.
9	**Patel K R.** Calcium antagonists in exercise-induced asthma. *Brit. Med. J.* 282:932-3, 1981.
11	**Pepys J & Hutchcroft B J.** Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Amer. Rev. Resp. Dis.* 112:829-59, 1975.
9	**Saarinen U M, Kajosaari M, Backman A & Siimes M A.** Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet* 2:163-6, 1979.
16	**Shore P A, Burkhalter A & Cohn V H.** A method for the fluorometric assay of histamine in tissues. *J. Pharmacol. Exp. Ther.* 127:182-6, 1959.
12	**Solley G O, Gleich G J, Jordon R E & Schroeter A L.** Late phase of immediate wheal and flare skin reaction—its dependence upon IgE antibodies. *J. Clin. Invest.* 58:408-20, 1976.
22	**Wide L, Bennich H & Johansson S G O.** Diagnosis of allergy by an in-vitro test for allergen antibodies. *Lancet* 2:1105-7, 1967.

Table 5: The C-2 1983 research fronts cited by core allergy journals. A = research front number. B = research front name. C = number of allergy core journals that cite the front. D = total citing articles from allergy core journals.

A	B	C	D
83-0012	Allergies and related disorders	6	102
83-0031	Identification of T-cell and B-cell subsets and their role in tumor immunotherapy	6	63
83-0406	Regulation of the IgA immune response	7	47
83-0275	Activity of neuromuscular blocking agents and histamine metabolism	5	40
83-0436	Measurement of pulmonary function and diseases, physiological states and drugs that affect it	6	38
83-0527	Prostaglandins, thromboxanes and other substances in platelet activation and function	6	35
83-1117	Allergic reactions and skin sensitivity to acrylate, nickel and other substances	1	34
83-0145	cDNA cloning, gene structure, RNA activity expression and protein structure	3	15
83-1343	Skin and respiratory tract response to aspirin	3	14
83-0175	Circulating immune complexes in patients with cancerous tumors, viral infection, lupus erythematosus and glomerulonephritis	3	12
83-0460	Pharmacokinetics of theophylline, aminophylline and caffeine	2	10

nals. As I've mentioned before, ISI's clustering system permits us to map and identify research areas in many ways.[49] Table 5 contains a ranked list of the 1983 *SCI/SSCI* research fronts whose core papers are cited by core allergy journals. The list gives us some indication of the emphasis in these core allergy journals. Similar analyses can be performed on any journal or group of journals. Quite often these analyses indicate the subject preferences of the editors. These com-

parative studies show considerable differences between journals that might be presumed to cover the same discipline.

As we have seen, allergy is an active and diverse area of research. The development of new research techniques will provide more information on the basic mechanisms of allergy and adverse reactions. Some of this research may substantiate the theories of clinical ecology, mentioned in part two of this essay,[1] or they may be entirely disproven. Certainly, more will be understood about the relationship between the mind and the immune system and the effect allergies have on behavior.

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REFERENCES

1. **Garfield E.** Allergies are nothing to sneeze at. Parts 1 & 2. *Current Contents* (13):3-14, 1 April 1985 and (15):3-12, 15 April 1985.
2. **King D S.** Can allergic exposure provoke psychological symptoms? A double-blind test. *Biol. Psychiat.* 16:3-19, 1981.
3. **Pearson D J & Rix K J B.** Allergomimetic reactions to food and pseudo-food-allergy. (Dukor P, Kallós P, Schlumberger H D & West G B, eds.) *Idiopathic, food-induced and drug-induced pseudo-allergic reactions.* New York: Karger, 1985. p. 59-105.
4. **Pearson D J.** Food allergy, hypersensitivity and intolerance. *J. Roy. Coll. Phys. Lond.* 19(3):154-62, 1985.
5. **Horton D J, Suda W L, Kinsman R A, Souhrada J & Spector S L.** Bronchoconstrictive suggestion in asthma: a role for airways hyperreactivity and emotions. *Amer. Rev. Resp. Dis.* 117:1029-38, 1978.
6. **Farr R S.** One definition of asthma. *Chest* 87(1, Suppl.):20S-21S, 1985.
7. **Buckley J M.** Asthma and depression. *Hosp. Pract.* 15(4):20; 25; 28, 1980.
8. **Norrish M, Tooley M & Godfrey S.** Clinical, physiological, and psychological study of asthmatic children attending a hospital clinic. *Arch. Dis. Child.* 52:912-7, 1977.
9. **McGovern J P & Knight J A.** Emotions as triggering episodes of allergy—emotional conditioning and polycyclic attacks. *Allergy and human emotions.* Springfield, IL: Charles C. Thomas, 1967. p. 31-42.
10. **Weiss E.** Psychoanalyse eines Falles von nervösem Asthma (Psychoanalysis in a case of nervous asthma). *Intern. Z. Psychoanal.* 8:440-55, 1922.
11. **Jones N F, Kinsman R A, Schum R & Resnikoff P.** Personality profiles in asthma. *J. Clin. Psychol.* 32:285-91, 1976.
12. **Creer T L & Kotses H.** Asthma: psychologic aspects and management. (Middleton E, Reed C E & Ellis E F, eds.) *Allergy: principles and practice.* St. Louis, MO: Mosby, 1983. Vol. 2. p. 1015-36.
13. **Nasr S J & Atkins R W.** Coincidental improvement in asthma during lithium treatment. *Amer. J. Psychiat.* 134:1042-3, 1977.
14. **Garfield E.** What do we know about depression? Parts 1-3. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 100-15; 157-63.
15. **Matussek P, Agerer D & Seifbt G.** Allergic disorders in depressive patients. *Compr. Psychiat.* 24:25-34, 1983.
16. **Wood K, Harwood J & Coppen A.** Platelet accumulation of histamine in controls, depressed and lithium-treated patients. *J. Affect. Disorders* 7:149-58, 1984.
17. **Kallner M.** Telephone communication. 24 September 1985.
18. **Sugerman A A, Southern D L & Curran J F.** A study of antibody levels in alcoholic, depressive and schizophrenic patients. *Ann. Allergy* 48:166-71, 1982.
19. **Garfield E.** What do we know about the group of mental disorders called schizophrenia? Parts 1 & 2. *Essays of an information scientist.* Philadelphia: ISI Press, 1984. Vol. 6. p. 188-96; 204-15.
20. **Dohan F C, Grasberger J C, Lowell F M, Johnston H T & Arbegast A W.** Relapsed schizophrenics: more rapid improvement on a milk- and cereal-free diet. (Abstract.) *Brit. J. Psychiat.* 115:595-6, 1969.
21. **Dohan F C & Grasberger J C.** Relapsed schizophrenics: earlier discharge from the hospital after cereal-free, milk-free diet. *Amer. J. Psychiat.* 130:685-8, 1973.
22. **Dohan F C, Harper E H, Clark M H, Rodrigue R B & Zigas V.** Is schizophrenia rare if grain is rare? *Biol. Psychiat.* 19:385-99, 1984.
23. **DeLisi L E, Weber R J & Pert C B.** Are there antibodies against brain in sera from schizophrenic patients? *Biol. Psychiat.* 20(1):110-5, 1985.

24. **Kinnell H G, Kirkwood E & Lewis C.** Food antibodies in schizophrenia. *Psychol. Med.* 12:85-9, 1982.
25. **McGuffin P, Gardiner P & Swinburne L M.** Schizophrenia, celiac disease, and antibodies to food. *Biol. Psychiat.* 16:281-5, 1981.
26. **Dohan F C.** Letter to editor. (Schizophrenia, celiac disease, gluten antibodies, and the importance of Beta.) *Biol. Psychiat.* 16:1115-6, 1981.
27. **Finn R & Cohen H N.** "Food allergy": fact or fiction? *Lancet* 1:426-8, 1978.
28. **Cummings N P & Bock S A.** Letter to editor. (Sensitivity to foods and additives: effect on behavior.) *JAMA—J. Am. Med. Assn.* 251:1209, 1984.
29. **Trites R L, Tryphonas H & Ferguson H B.** Diet treatment for hyperactive children with food allergies. (Knights R M & Bakker D J, eds.) *Treatment of hyperactive and learning disordered children.* Baltimore, MD: University Park Press, 1980. p. 151-63.
30. **Feingold B F.** *Why your child is hyperactive.* New York: Random House, 1975. 211 p.
31. **Mattes J A & Gittelman R.** Effects of artificial food colorings in children with hyperactive symptoms. *Arch. Gen. Psychiat.* 38:714-8, 1981.
32. **Weiss B, Williams J H, Margen S, Abrams B, Caan B, Citron L J, Cox C, McKibben J, Ogar D & Schultz S.** Behavioral responses to artificial food colors. *Science* 207:1487-9, 1980.
33. **Weiss B.** Food additives and environmental chemicals as sources of childhood behavior disorders. *J. Amer. Acad. Child Psychiat.* 21:144-52, 1982.
34. **Rapp D J.** Does diet affect hyperactivity? *J. Learn. Disabil.* 11:383-9, 1978.
35. **Taylor E.** Food additives, allergy and hyperkinesis. *J. Child Psychol. Psychiat.* 20:357-63, 1979.
36. **National Institutes of Health.** Defined diets and childhood hyperactivity. *JAMA—J. Am. Med. Assn.* 248:290-2, 1982.
37. **Monro J, Carini C & Brostoff J.** Migraine is a food-allergic disease. *Lancet* 2:719-21, 1984.
38. **Egger J, Carter C M, Wilson J, Turner M W & Soothill J F.** Is migraine food allergy? *Lancet* 2:865-9, 1983.
39. **Ratner D, Shneyour A, Eshel E & Teitler A.** Elevated IgM in dietary migraine with lactase deficiency. *Isr. J. Med. Sci.* 20:717-9, 1984.
40. **Crayton J W, Stone T & Stein G.** Epilepsy precipitated by food sensitivity: report of a case with double-blind placebo-controlled assessment. *Clin. Electroencephalogr.* 12:192-8, 1981.
41. **Pearson D J, Rix K J B & Bentley S J.** Food allergy: how much in the mind? *Lancet* 1:1259-61, 1983.
42. **Ader R.** Psychosomatic and psychoimmunologic research. *Psychosom. Med.* 42:307-21, 1980.
43. **Solomon G F & Amkraut A A.** Psychoneuroendocrinological effects on the immune response. *Annu. Rev. Microbiol.* 35:155-84, 1981.
44. **Harrell R F, Capp R H, Davis D R, Peerless J & Ravitz L R.** Can nutritional supplements help mentally retarded children? An exploratory study. *Proc. Nat. Acad. Sci. US—Biol. Sci.* 78:574-8, 1981.
45. **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.
46. **Lichtenstein L M, Valentine M D & Sobotka A K.** Insect allergy: the state of the art. *J. Allerg. Clin. Immunol.* 64:5-12, 1979.
47. **Hunt K J, Valentine M D, Sobotka A K, Benton A W, Amodio F J & Lichtenstein L M.** A controlled trial of immunotherapy in insect hypersensitivity. *N. Engl. J. Med.* 299:157-61, 1978.
48. **Wide L, Bennich H & Johansson S G O.** Diagnosis of allergy by an in-vitro test for allergen antibodies. *Lancet* 2:1105-7, 1967.
49. **Garfield E.** ABCs of cluster mapping. Parts 1 & 2. Most active fields in the life and physical sciences in 1978. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 634-49.