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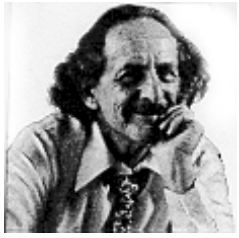

Current Comments®

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

Allergies Are Nothing to Sneeze At: Part 1. Epidemiology and Etiology

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Allergies are a common problem, affecting at least 15 percent of Americans and probably comparable numbers in other industrialized countries—at least 100 million people worldwide. Symptoms range from a runny nose to a life-threatening anaphylactic reaction. The causes of those allergies are as diverse as the symptoms. This first of a three-part essay will discuss the immune mechanisms that cause allergic reactions and the factors that predispose some of us to them. In the next part, we will focus on diagnosis and treatment. The third part will deal with the behavioral aspects of allergic disorders.

Allergy is an "abnormal" reaction to ordinarily harmless substances. It is synonymous with hypersensitivity. The word allergy was coined in 1906 by the Austrian physician, Clemens Baron von Pirquet.[1] The term is derived from the Greek words *allos* meaning other and *ergon* meaning work or action. This presumably implies an unusual or inappropriate reaction to a stimulus.

A disorder of the immune system, allergy is frequently described as immunity "gone wrong." According to Elmer Bendiner, contributing editor, *Hospital Practice*, New York, von Pirquet gave allergy a dual meaning. It covered the body's reactions to foreign substances, regardless of whether that reaction was exaggerated as in hypersensitivity, or diminished as in immunity.[2] Hypersensitivity and immunity were considered by von Pirquet to be opposite forms of allergy. Later on the term was associated almost exclusively with the hypersensitivity reaction. More recently, K. Frank Austen, Department of Medicine, Harvard Medical School, Boston, suggested that the broad term allergy be replaced by the more specific designation "diseases of immediate hypersensitivity."[3] Immediate hypersensitivity refers to allergic reactions that are visible within minutes or a few hours.

That the human body is not compatible with all that exists in its environment has been recognized since antiquity. In fact, deaths due to stings from bees and wasps have been reported for centuries. R.A. Wirtz, Department of Entomology, Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, Washington, DC, indicates that one of the earliest documented cases occurred in 2641 BC when, according to the hieroglyphics found in his tomb, King Menes of Egypt died from a wasp or hornet sting.[4]

Asthma is one of the oldest forms of chronic allergy. In a review of the history of asthma, E.R. McFadden, then Director of Research, Shipley Institute of Medicine, Brigham, Massachusetts, and J.B. Stevens, Respiratory Disease Division, Brigham and Women's Hospital, Boston, noted that asthma was first discussed, in detail, in the early Chris-

tian era. However, it was not until the early part of this century that asthma was considered a distinct clinical entity—the pulmonary response to previous sensitization.[5]

The immune system generally serves a protective function, distinguishing between self and nonself. This system determines whether foreign tissues, proteins, and other large molecules are harmless or potentially harmful. The first step in the immune response is to recognize a specific antigen, or foreign substance. This is accomplished by a type of white blood cell called the lymphocyte. Two types of lymphocytes act in this capacity, T cells and B cells.

When an allergen or a substance capable of causing an allergic reaction enters the body, both T and B cells recognize it as being foreign to the body. T cells are called helper cells because they help the B lymphocytes to proliferate, or increase in number. According to J. John Cohen, Departments of Microbiology and Immunology and Medicine, University of Colorado Health Sciences Center, Denver, T cells pass a signal to B cells to divide and differentiate into antibody-secreting plasma cells that produce large numbers of antibodies.[6] All antibodies belong to a class of proteins known as immunoglobulins. There are five major types of immunoglobulins, each designated by a letter: IgA (alpha), IgD (delta), IgG (gamma), IgE (epsilon), and IgM (mu). The immunoglobulins differ in chemical and physical properties. However, we will only be concerned in this discussion with classical allergy diseases that are IgE-mediated, immediate hypersensitivity reactions.

Once an allergen enters the body, IgE is the main antibody responsible for the allergic reactions that plague so many people. IgE was first associated with the immediate hypersensitivity reaction in 1967 when Kimishige Ishizaka and Teruko Ishizaka, a husband and wife research team, then of the Children's Asthma Research Institute and Hospital, Denver, isolated it from the blood serum of hay fever sufferers.[7] It was this work that made Teruko Ishizaka one of the most-cited female scientists for the period 1965-1978.[8] The Ishizakas are now in the Subdepartment of Immunology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Although IgE is a minor immunoglobulin class comprising a small part of total circulating immunoglobulins, Kent A. Knauer and N. Franklin Adkinson, Jr., Department of Medicine, Johns Hopkins University School of Medicine, indicate that blood levels are three to five times higher in allergic than in normal patients.[9] In fact, Robert A. Barbee and colleagues, Division of Respiratory Sciences, University of Arizona College of Medicine, Tucson, noted that future allergies can be predicted in children by the rate of development of blood serum IgE levels during the first years of life.[10] However, not all allergies raise the total IgE level.

Symptoms of IgE-mediated food allergies are not to be confused with nonimmunologic adverse reactions to food. For example, in lactose intolerance there is a deficiency of the enzyme lactase, which aids in the digestion of lactose, a sugar found in milk.

IgE functions by sensitizing an effector cell, which, in response to a stimulus, secretes mediators of immediate hypersensitivity. Two common effector cells are mast cells, found in connective tissue, and basophils, a type of white blood cell. Both have thousands of receptors for IgE molecules. According to Timothy J. Sullivan, Department of Internal Medicine, University of Texas Health Science Center, Dallas, and Anthony Kulczycki, Jr., Division of Immunology, Washington University School of Medi-

cine, St. Louis, Missouri, the biologic function of IgE in allergy results from its affinity for mast cells and for basophils.[11]

When the appropriate allergen is encountered, the IgE antibodies, which are sitting on mast cells and basophils, react with the allergen. As this happens these cells release chemicals that mediate the allergic reaction.[11]

The formation and release of these chemical mediators are prerequisites for allergy symptoms. There are several common mediators. One is histamine, which is released from mast cells found in the skin, mucosa of the nose, bronchi, and gut, and also from basophils. The symptoms resulting from histamine release depend on the tissue into which it is released. For example, Dean D. Metcalfe and colleagues, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), and Biochemistry Department, Armed Forces Radiobiology Research Institute, National Naval Medical Center, Bethesda, noted that histamine causes itching and flushing in the skin and stuffiness in the nose.[12] Histamine also causes smooth muscle contraction in the bronchi of the lungs, which may make breathing difficult during an allergy attack. In the essay on ulcers, we discussed the two types of histamine receptors, H_1 and H_2.[13] Drugs like cimetidine (Tagamet) and ranitidine (Zantac) are H_2 antagonists. Most allergy pills like Actifed contain H_1 antagonists.

Other recently identified chemical mediators of the allergic reaction, synthesized in mast cells and leukocytes, are leukotrienes, some of which are potent bronchoconstrictors. In fact, Paul Buisseret, then of the Department of Medicine, School of Medicine, Louisiana State University Medical Center, New Orleans, observed that leukotrienes are 100 to 1,000 times as potent as histamine in causing constriction of the bronchi of the lungs.[14] Leukotrienes also cause inflammation by stimulating the local leakage of fluid from blood vessels. In 1979, the structure of the leukotrienes was defined by Nobel laureate Bengt Samuelsson and colleagues, Department of Physiological Chemistry, Karolinska Institute, Stockholm, Sweden. They called these chemical compounds leukotrienes because they were found in leukocytes and contain three double bonds (trienes), separated by single bonds.[15,16]

Prostaglandins have also been implicated in the allergic reaction. Buisseret indicated that prostaglandins, also synthesized in leukocytes, act in the contraction of smooth muscle in the airways or intestine, the dilation of small blood vessels, and cause inflammation by increasing the permeability of small blood vessels to water and plasma proteins.[14] They also initiate the secretion of thick, sticky mucus, and contribute to the itching skin and pain associated with the allergic reaction.

According to Stephen I. Wasserman, Department of Medicine, School of Medicine, University of California, San Diego, Medical Center, the degree of severity of the allergic reaction will depend on the local target organ sensitivity as well as the amounts and ratios of specific mediators formed and released.[17] Symptoms of allergy can range from a mild local irritation to the life-threatening systemic collapse of anaphylactic shock. In apposition to prophylaxis, the term anaphylaxis, or anaphylactic shock, denotes an extreme hypersensitivity reaction in which blood vessels become dilated and peripheral vascular collapse occurs because of inadequate blood pressure.

Kenneth P. Mathews, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, confirms that allergies are a relatively com-

mon problem. He recently reported that about 9 percent of all visits to a physician are for symptoms of one of the common allergies.[18] Edward W. Hein and Rajeev Kishore, Section of Pediatric Allergy and Clinical Immunology, Cleveland Clinic Foundation, Ohio, noted that over 20 percent of all children are allergic to something. In fact, allergy is the leading cause of school absenteeism in the US.[19]

Of the 35 million Americans who suffer from allergies, about 8.9 million have asthma with or without hay fever; 14.7 million have hay fever alone; and 11.8 million have other allergy problems such as eczema and hives or food, drug, or insect sting hypersensitivity.[18] A 1982 study by K.K. Eaton, Inhalant Allergy Clinic, Royal Berkshire Hospital, Reading, England, compared the incidence of allergy, in a population of over 11,000, in 1974 and 1979. He found a significant increase in the total incidence of allergy.[20]

According to David G. Marsh and colleagues, Department of Medicine, Johns Hopkins University School of Medicine, the incidence of allergy increases with age until about 20 to 24 years when it begins a gradual decline.[21] Barbee also reported that IgE levels decline with age. Females have significantly lower IgE levels than males at all ages.[10]

The occurrence of allergy varies considerably worldwide. Epidemiologic studies comparing isolated rural populations with urban groups find less allergy-associated illness in the isolated groups. For example, H.R. Anderson, then of the Papua New Guinea Institute of Medical Research, Goroka, found the incidence of asthma to be lower in the rural New Guinea Highlands village of Lufa than in the town of Goroka.[22] When the disease did occur in the rural population, it generally affected those who had been exposed to European communities. A study of immediate hypersensitivity reactions in Amerindians from the Venezuelan sector of the Amazon basin by Neil R. Lynch and colleagues, Panamerican Centre for Research and Training in Leprosy and Tropical Diseases, Instituto Nacional de Dermatología, Universidad Central de Venezuela, and Departamento de Tuberculosis, Ministerio de Sanidad y Asistencia Social, Caracas, found only a little over 6 percent positive reactions to local environmental allergens.[23] The authors suggest that these populations have an inhibited expression of allergy due to mast-cell saturation with IgE as a result of intense parasitic infection. However, Jeanne M. Smith, Division of Allergy and Immunology, University of Iowa, Iowa City, noted that this has not been supported by more recent research.[24]

While the prevalence may differ between rural and urban areas, manifestations may differ according to geographic location. Hives are not as common an allergic symptom in the West as in China where they are considered to be a leading allergic disorder, according to S-t. Yeh, Department of Allergy, Capital Hospital, Chinese Academy of Medical Sciences, Beijing.[25] Smith noted that asthma is uncommon in American Indians, Eskimos, and people of the New Guinea Highlands and Gambia;[26] in European and American populations, the incidence varies between communities.

Eaton's study also found sex differences in the manifestation of allergy. Females complained more frequently of drug allergies, eczema, and hives, while males showed a greater incidence of hay fever and asthma.[20] In a study of 600 allergic patients, Nils E. Eriksson and colleagues, Department of Medicine, Lanssjukhuset, Halmstad; Department of Allergology, Medical Clinic I, Sahlgren Hospital, Gothenburg; and Pediatric Department, Malmö General Hospital,

Sweden, reported that food hypersensitivity is more common in women than in men.[27]

According to N.-I. Max Kjellman, Department of Pediatrics, University Hospital, Linkoping, Sweden, genetic makeup is the most important predisposing factor in the development of allergy. He reported that about 10 percent of seven-year-old children develop allergies if neither parent is allergic. Where one parent is allergic 20 percent of the children are affected. But when both parents suffer from allergies, 42 percent of the children developed allergies.[28]

In fact, Smith noted that of children under 10 who developed allergies, 88 percent had close relatives with allergies.[26] The age at onset of disease plays a significant role in the development of future allergies. However, adult-onset respiratory allergy is frequently less severe and occurs less frequently than that which occurs in the young. In adult-onset respiratory allergy, IgE levels are likely to be normal, yet it is probably the same disease as occurs in young onset. The pioneer allergists R.A. Cooke and A. Vander Veer, then with the Post Graduate Medical School and Hospital, New York, suggested that this is associated with lesser degrees of genetic susceptibility in the adult-onset disease where there was no family history of allergy than in that which begins in childhood.[29]

Genetic predisposition to certain allergies is borne out by twin studies. Monozygotic twins are genetically similar and they share a similar environment. A study by Russell J. Hopp and colleagues, Department of Medicine, Creighton University School of Medicine, Omaha, Nebraska, showed that both monozygotic twins generally have similar histories of allergic disease, total serum IgE levels, and other indirect measures of allergy.[30] Dizygotic twins who share only a portion of their genes, on the other hand, generally have a dissimilar history of allergic disease and indirect measures of allergy show differences within the pair. We've recently reviewed twin studies and their contribution to human genetics.[31] However, we did not discuss the use of twins to investigate allergic disorders.

A 1976 study by J.W. Gerrard and colleagues, Department of Pediatrics, University of Saskatchewan, Canada, found that not only is there a genetic predisposition to allergy, but the expression of that allergy also has a familial tendency.[32] For example, they found a strong association between asthma in the parent and asthma in the child. The same association applied for hay fever and other forms of allergy.

Although there is a genetic predisposition to certain allergies, other associated risk factors have also been found. Risk factors are generally environmental elements that increase the likelihood of expression of clinical allergy. For example, a 1979 study by Oscar L. Frick and colleagues, University of California, San Francisco, Kaiser-Permanente Medical Center, and San Francisco General Hospital, found that children with a genetic tendency to allergies generally develop them after a minor viral infection.[33] However, a similar study by Ilpo Suoniemi and colleagues, Hospital for Allergic Diseases, Helsinki University Central Hospital, and Department of Pulmonary Diseases, Tiuru Hospital, Tiuruniemi, Finland, found that exposure to allergens during the first six months of life is a major risk factor for later development of allergies.[34] Infections during the first year of life were found to be minor risk factors.

Another factor that is thought to play a role in the development of allergies is early infant feeding practices. However, the hypothesis that breast feeding during

the first few weeks of life provides some protection against future allergies is still controversial. R.K. Chandra, Department of Pediatrics, Memorial University of Newfoundland, St. John's, Newfoundland, Canada, reported that six weeks of exclusive breast feeding is effective in lowering the incidence of allergy in genetically susceptible infants.[35] However, Ulla M. Saarinen and colleagues, Children's Hospital, University of Helsinki, Finland, indicated that breast feeding must continue for six months in order to nullify the hereditary tendency to develop allergies.[36] The study by Michael S. Kramer and Brenda Moroz, Departments of Pediatrics, Dermatology, and Epidemiology and Health, McGill University, Montreal, Canada, found no evidence for the protective effect of breast feeding in preventing eczema.[37] A 1983 review of various papers on this topic led Michael L. Burr, MRC Epidemiology Unit, Cardiff, Wales, to conclude that evidence tends to favor the hypothesis that nonbreast-fed infants have an increased risk of allergic disease.[38]

Although the role of breast feeding in preventing future allergies is still controversial, Saarinen and colleagues hypothesize that human milk protects the gastrointestinal tract from the entrance of foreign antigens.[39] The researchers found that birch pollen allergy did not occur in children weaned to cow-milk based infant formula during their first birch pollen season. This also is true for grass pollen. Saarinen and colleagues suggest that this occurs because the starting formula is stressful for the immune system and accelerates synthesis of both IgA and IgE. Thus, little immunologic capacity remains for production of antibodies to the pollen allergens.

Another potential risk factor is exposure to allergens in the first months of life. F. Björkstén and colleagues, Hospital for Allergic Diseases, Helsinki University Central Hospital, and Finnish Forest Research Institute, Helsinki, found that patients with birch pollen allergy were born more frequently during the birch pollen season.[40] They suggest that exposure to pollen in the first six months of life increases the risk of pollen allergy for the next 20 years. A similar study by J. Korsgaard and R. Dahl, Department of Respiratory Diseases, Århus Kommunehospital, Denmark, reported that patients born in the season when house dust mites are most abundant have a 40 percent greater chance of developing allergy to these mites.[41] These studies demonstrate the importance of environmental factors in controlling the development of allergic disease in genetically susceptible individuals.

Most research on allergies is directed toward understanding components of the immune system involved in the allergic response. However, a recent study by Michael Russell and colleagues, Brain-Behavior Research Center, Sonoma Developmental Center, University of California, Eldridge, found that conditioned learning can enhance the immune response to allergens.[42] When a stimulus that is not normally associated with an allergic reaction was paired with an allergen, guinea pigs later showed blood plasma histamine increases on presentation of the neutral stimulus alone. This implies that allergic reactions can be elicited by association, and this should be included in studies of the development and treatment of allergies.

While behavioral considerations may not be part of the traditional allergy practice, clinical ecology is a relatively new field that emphasizes the psychological as well as physical aspects of allergy. According to Iris R. Bell, Department of Psychiatry, Langley Porter Psychiatric Institute, University of California, San

Table 1: The *SCI®/SSCI®* 1983 research fronts on allergies. A=number. B=name. C=number of core papers. D=number of 1983 citing papers.

A	B	C	D
83-0014	Studies of asthma, eczema and atopic dermatitis related to house dust, mites and food allergens	10	66
83-0816	Immunotherapy of asthma and other allergic diseases; epidemiology and genetics of allergic reactivity	2	16
83-1271	Mast cell and T cell mediated late and delayed type hypersensitivity in cutaneous inflammation, asthma and allergies	8	90
83-1355	Anesthesia by intravenous infusion with etomidate, halothane, enflurane, althesin, methohexitone and other agents; and role in adrenocortical inhibition and allergic reactions	32	108
83-1451	Immunochemical characterization of allergens via electrophoresis	5	99
83-1726	Circulating immune complexes in allergic alveolitis or farmers lung; occupational lung disease and avian exposure	7	29
83-2367	Clinical studies of Wegeners granulomatosis and associated lymphomatoid allergic vasculitis	25	135
82-2897	Atopic allergies in infants breast fed or given cow's milk; prevention of immunological intolerance	9	50
83-3761	Role of prostaglandins in food intolerance and allergies, and irritable bowel syndrome	3	16
83-3807	Use of lung function testing in the diagnosis of occupational asthma and other respiratory allergies induced by diisocyanate, colophony and other substances	3	14
83-3966	Allergy to Hymenoptera venom and immunotherapy with IgG and IgE antibodies	9	43
83-4178	Effect of nifedipine, verapamil, calcium antagonists and histamine on bronchoconstriction; exercise and allergen-induced asthma	3	20
83-4461	Allergic activity of lanolin, triethanolamine and chloracetamide	4	7
83-4686	Pharmacotherapy of allergic rhinitis with beclomethasone, budesonide and cyclomethasone	5	18
83-5211	Contact dermatitis and sensitizing potential of acrylate in guinea pigs; safety testing for allergic potential	6	31
83-6064	Isolation and purification by affinity chromatography of allergic response antibodies that react with alcuronium and other muscle relaxant drugs	3	26
83-7017	*Characterization of contact dermatitis; allergic reactions and skin sensitivity* to nickel and other substances	6	21
83-7036	Characterization of allergic responses to fish and other substances and their role in contact urticaria	4	24

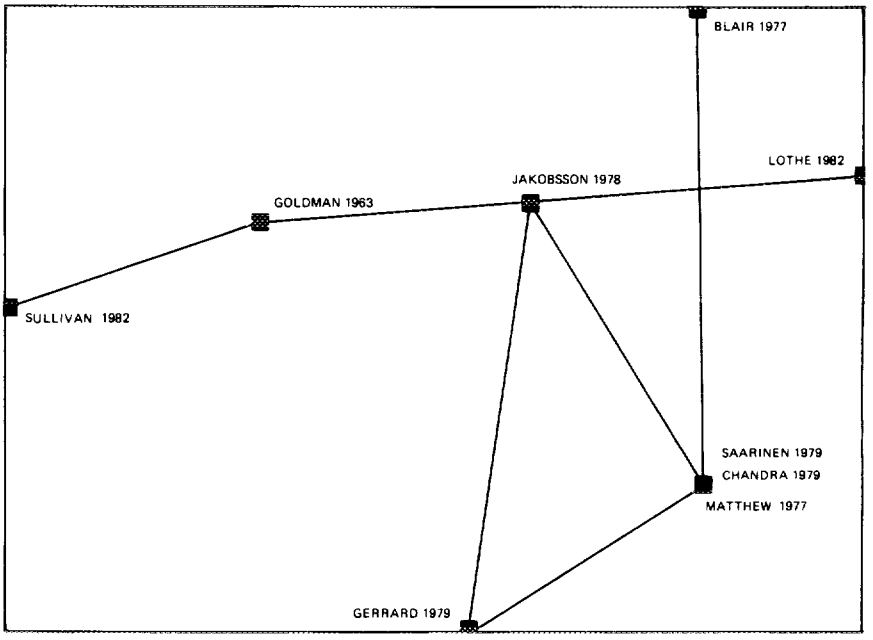
Francisco, School of Medicine, clinical ecology espouses a holistic approach that includes the total stress load and the frequency of exposure and adaptation to the allergen.[43] (p. 16) However, Bell emphasizes that there are immune mechanisms other than IgE mediated, and possibly nonimmune events, that cause symptoms that look like allergy and may lead to behavioral manifestations.

One of the early proponents of clinical ecology was Theron Randolph, an allergist who, with four colleagues, in 1965, founded the Society for Clinical Ecology. Randolph and other clinical ecologists were the first to include in the definition of allergy adverse reactions to common foods and chemicals that appear in our increasingly synthetic environment. We discussed the impact of indoor pollution on health in a previous essay.[44] More will be said about clinical ecology in the second part of this essay.

Research Fronts on Allergies

Thousands of papers have been published on "allergies" in recent years. *SCISEARCH®* produced over 1,000 papers per year for a 10-year period using the term "allerg." A search of ISI®'s files shows that there are at least 18 research fronts on or related to allergy. These are listed in Table 1. Were we to list all the research fronts on asthma, we would add

Figure 1: Multidimensional scaling map showing co-citation links between core papers for the 1983 *SCI*® research front, "Atopic allergies in infants breast fed or given cow's milk; prevention of immunological intolerance."



Key

Blair H. Natural history of childhood asthma. *Arch. Dis. Child.* 52:613-9, 1977.

Chandra R K. Prospective studies of the effect of breast feeding on incidence of infection and allergy. *Acta Paediat. Scand.* 68:691-4, 1979.

Gerrard J W. Allergy in breast fed babies to ingredients in breast milk. *Ann. Allergy* 42:69-72, 1979.

Goldman A S, Anderson D W, Sellers W A, Saperstein S, Knlker W T, Halpern S R & collaborators. Milk allergy. I. Oral challenge with milk and isolated milk proteins in allergic children. *Pediatrics* 32:425-43, 1963.

Jakobsson I & Lindberg T. Cow's milk as a cause of infantile colic in breast-fed infants. *Lancet* 2:437-9, 1978.

Lothe L, Lindberg T & Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics* 70:7-10, 1982.

Matthew D J, Norman A P, Taylor B, Turner M W & Soothill J F. Prevention of eczema. *Lancet* 1:321-4, 1977.

Saarinen U M, Backman A, Kajosaari M & Siimes M A. Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet* 2:163-6, 1979.

Sullivan T J, Yecles L D, Shatz G S, Parker C W & Wedner H J. Desensitization of patients allergic to penicillin using orally administered β-lactam antibiotics. *J. Allerg. Clin. Immunol.* 69:275-82, 1982.

another 21. One research front on allergy is #83-0816, "Immunotherapy of asthma and other allergic diseases; epidemiology and genetics of allergic reactivity." The papers by Marsh[21] and Anderson[22] are the two core works that help identify this small front in which 18 papers were published in 1983. The paper by Lynch[23] was retrieved because it cites both of these "core" papers.

The papers mentioned earlier by Chandra[35] and Saarinen[36] are two of the nine core documents identifying research front #83-2897, "Atopic allergies in infants breast fed or given cow's milk; prevention of immunological intolerance." Figure 1 provides a multidimensional scaling (MDS) map of the co-citation relationship between these papers. The lengths of the connecting lines are inversely proportional to the co-citation strength.[45]

Another research front, #83-0014, concerns "Studies of asthma, eczema and atopic dermatitis related to house dust, mites and food allergens." Figure 2 is an MDS map for the 10 core papers of this research front. Two papers were frequently cited by papers in this front. One is "A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema" by D.J. Atherton and colleagues, Hospital for Sick Children, Institute of Child Health, and London School of Hygiene and Tropical Medicine.[46] The other by K. Aas, Allergy Institute, Voksentoppen, and Allergy Unit, Paediatric Research Institute, Rikhospitalet, University of Oslo, Norway, is entitled, "The diagnosis of hypersensitivity to ingested foods."[47] Both were cited by 15 of the 66 papers published on this topic in 1983.

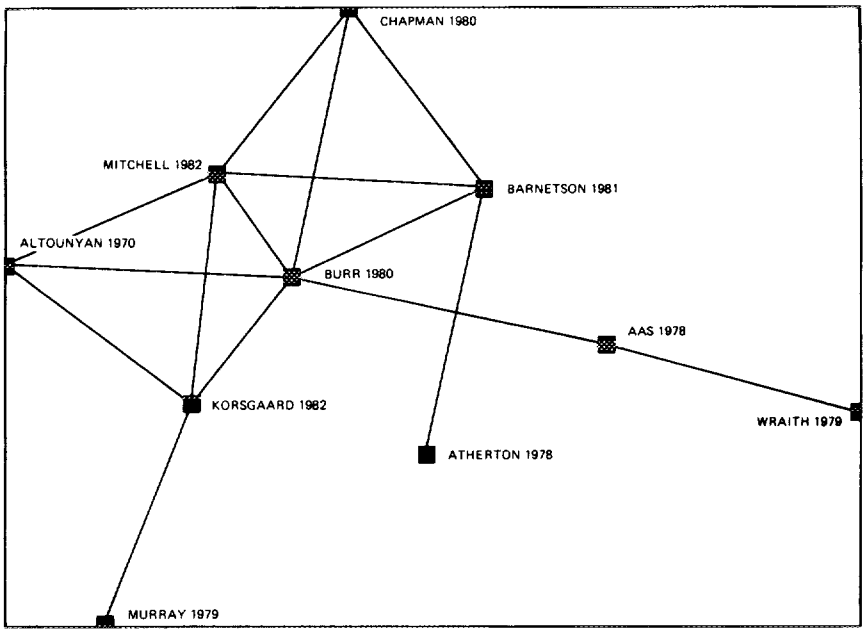
The largest research front dealing with allergies is #83-2367, "Clinical studies of Wegeners granulomatosis and associated lymphomatoid allergic vasculitis." The 1978 publication of an NIH conference on vasculitis, moderated by Anthony S. Fauci, National Institute of Allergy and Infectious Diseases, NIH, is the most-cited core paper. It was cited by 63 of the 135 current citing papers on this topic for 1983.[48]

Research fronts can be clustered in the same way as the core papers that define them. These clusters of research fronts show the citation links between various areas of research and even between whole disciplines. Research front #83-0014 is one of a group of closely linked research fronts shown in the C-2 level map in Figure 3. As can be seen in the map, research front #83-0013, "Immunological studies and characterization of hen egg white allergen and other allergen extracts," is closely related to research front #83-4180, "Assays for IgE and IgG antibodies to foods, bee venom antigens, pollen extracts, tetanus toxoid and other allergens; enzyme linked immunosorbent assay, radioallergosorbent assay and monkey PCA."

In creating these higher-level maps, we move from the specific to the more generic. For example, the C-1 level map shows relationships between individual core papers. The C-2 level map connects various C-1 research fronts. By looking at these multilevel maps, one can see the relationship between various levels within a discipline and the connection of that discipline to other areas of science.

Some of the primary journals that have published articles on allergies are found in Table 2. As the list indicates, allergy articles are generally published in clinical journals that specialize in allergy and clinical immunology research. Also included in Table 2 is the impact factor for each journal as reported in our 1983 *Journal Citation Reports®* (*JCR™*). Impact was calculated by dividing the number of citations a journal's 1981 and 1982

Figure 2: Multidimensional scaling map of the co-citation relationships between the core papers in the 1983 *SCI*® research front, "Studies of asthma, eczema and atopic dermatitis related to house dust, mites and food allergens."



Key

Aas K. The diagnosis of hypersensitivity to ingested foods. *Clin. Allergy* 8:39-50, 1978.

Altounyan R E C. Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease. (Pepys J & Frankland A W, eds.) *Disodium cromoglycate in allergic airways disease. Proceedings of the Symposium of the Royal Society of Medicine*, 5 March 1969, London, UK. London: Butterworths, 1970. p. 47-53.

Atherton D J, Soothill J F, Sewell M, Wells R S & Chilvers C E D. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet* 1:401-3, 1978.

Barnetson R S C, Merrett T G & Ferguson A. Studies on hyperimmunoglobulinaemia E in atopic diseases with particular reference to food allergens. *Clin. Exp. Immunol.* 46:54-60, 1981.

Burr M L, Dean B V, Merrett T G, Neale E, Leger A S S & Verrier-Jones E R. Effects of anti-mite measures on children with mite-sensitive asthma: a controlled trial. *Thorax* 35:506-12, 1980.

Chapman M D & Platts-Mills T A E. Purification and characterization of the major allergen from *Dermatophagoides pteronyssinus*-antigen P_1. *J. Immunol.* 125:587-92, 1980.

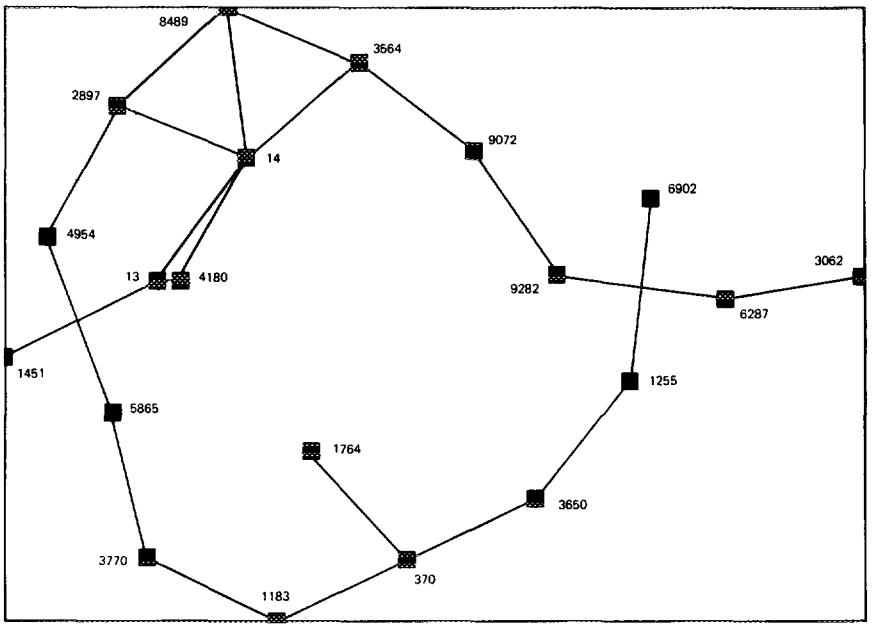
Korsgaard J. Preventive measures in house-dust allergy. *Amer. Rev. Resp. Dis.* 125:80-4, 1982.

Mitchell E B, Chapman M D, Pope F M, Crow J, Jouhal S S & Platts-Mills T A E. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1:127-30, 1982.

Murray A B & Zuk P. The seasonal variation in a population of house dust mites in a North American city. *J. Allerg. Clin. Immunol.* 64:266-9, 1979.

Wraith D G, Merrett J, Roth A, Yman L & Merrett T G. Recognition of food-allergic patients and their allergens by the RAST technique and clinical investigation. *Clin. Allergy* 9:25-36, 1979.

Figure 3: C_2 level map for cluster 12,"Allergies and related disorders," showing links between research fronts. A = 1983 research front number. B = research front title.



A	B
83-0013	Immunological studies and characterization of hen egg white allergen and other allergen extracts
83-0014	Studies of asthma, eczema and atopic dermatitis related to house dust, mites and food allergens
83-0370	Biochemical isolation and characterization of human, horse and rat ferritin; subunits, endocytosis and iron metabolism in the liver
83-1183	Role of siderophores and transferrin in the interaction of iron with *Escherichia coli* and other microbes
83-1255	*In vitro* regulation of hematopoietic stem cells; differentiation of normal and leukemic bone marrow cells in long term cultures by colony-stimulating factors, suppressors, viruses and radiation
83-1451	Immunochemical characterization of allergens via electrophoresis
83-1764	Subunit dimers in apoferritin and iron storage; structure and metal binding including beryllium
83-2897	Atopic allergies in infants breast fed or given cow's milk; prevention of immunological intolerance
83-3062	Retention of inhaled particles of plutonium-241 and the deposition of sulfuric acid in the respiratory tracts of beagles and rats
83-3564	IgA and IgE immune complexes associated with food allergy; oral sodium chromoglycate for prevention of food allergy
83-3650	Action of lactoferrin, transferrin and acidic isoferritins in disease regulation and granulocyte-macrophage production
83-3770	Absorption of iron bound to lactoferrin, zinc and other supplements in cow's milk and human milk
83-4180	Assays for IgE and IgG antibodies to foods, bee venom antigens, pollen extracts, tetanus toxoid and other allergens; enzyme linked immunosorbent assay, radioallergosorbent assay and monkey PCA
83-4954	Infant growth and other factors in the evaluation of the effect of breast feeding on infants

A	B
83-5865	Effect of processing and storage on enzymes, vitamins and lipids of human milk
83-6287	Models for estimating human inhalation exposure to americium oxide and other actinide compounds
83-6902	Growth factors from platelets and proliferation of hematopoietic cells *in vitro*
83-8489	Diagnosis based upon food allergy and asthma in infants; allergens and immune complexes
83-9072	Protein, antigens, antibodies and other factors in bovine milk associated with absorption, celiac disease and other aspects of milk intolerance
83-9282	Absorption and metabolism of plutonium, the actinides and other radionuclides in the gastrointestinal and other tissue systems of rats and of man

Table 2: Selected list of allergy journals indexed by ISI®. A = journal title and first year of publication. B = impact factor.

A	B
Allergologia et Immunopathologia, 1972	.088
Allergologie, 1978	—*
Allergy, 1948 (formerly Acta Allergologica)	1.47
Annals of Allergy, 1943	0.76
Clinical Allergy, 1971	1.46
Clinics in Immunology and Allergy, 1981	—*
Contact Dermatitis, 1975	0.63
International Archives of Allergy and Applied Immunology, 1950 (formerly Journal of Allergy)	1.26
Journal of Allergy and Clinical Immunology, 1929	3.38
Journal of Asthma, 1963	0.18
Monographs in Allergy, 1966	2.93
Progress in Allergy, 1939	6.33
Revue Francaise d'Allergologie et Immunologie Clinique, 1961	0.16

*Added in 1982.

articles received in 1983 by the number of articles it published in that two-year period.

The recent activity in the allergy and clinical immunology literature suggests that allergy is an active and productive field of research. The second part of this essay will discuss the practical applications of allergy research in the diagnosis and treatment of allergy.

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