

The ALLERGY ARCHIVES

Pioneers and Milestones

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Anaphylaxis and the American Academy of Allergy, Asthma, and Immunology

Our challenge was to identify the contributions of members of the American Academy of Allergy, Asthma and Immunology (AAAAI) to our current understanding of anaphylaxis. There are no organized archives dealing directly with this subject. We therefore began with a search of relevant journals for members' scientific contributions to anaphylaxis research, beginning in 1923, the year in which the 2 founding organizations of the AAAAI originated. We continued through 1929, when *The Journal of Allergy* was first published, through 1943, when our founding organizations amalgamated to form the American Academy of Allergy, to the present. As well, AAAAI members and Fellows were asked, through invitations including a broadcast e-mail and advertisements in *The Journal of Allergy and Clinical Immunology* and *Academy News*, to submit 250-word retrospective accounts of their published contributions to anaphylaxis research.

We begin with a quote from the January 1944 issue of *The Journal of Allergy*¹ noting, "As *The Journal of Allergy* enters its 15th year, it does so under new and auspicious circumstances. The two established national allergy societies which this publication represented have become one. This merger, in effect, was little more than a formality, for there was a large interlocking membership, and the aims and purposes of each organization were essentially identical. The American Academy of Allergy thus came into being by unanimous consent, its bylaws based on those of its organizations. By virtue of this roster of members, it represents leadership in the clinical and scientific aspects of allergy in this country." Thus begins our journey attempting to document the contributions of the members of the organization, known since 1995 as the AAAAI, to our understanding of anaphylaxis.

THE EARLY YEARS

It is difficult to ascertain which years were indeed the early ones, but arbitrarily we have chosen to use the dates from our origins to the mid-1960s, when it

was discovered that reaginic antibody was IgE. During these years, detailed case reports and small case series of patients with anaphylaxis appeared from time to time in *The Journal of Allergy* and other leading journals of the time, often describing sudden death after injection of "foreign protein." Causative agents involved diphtheria toxin antitoxin (horse serum), blood products, or allergens used for skin testing and immunotherapy; for example, in 1935, Dr H. J. Friedman described the death of a 6-year-old boy within 8 minutes of a skin test to horse serum.

In the 1930s, Dr Robert Cooke described allergic reactions induced by immunization with tetanus toxoid. He was also one of the first to describe allergic drug reactions. He introduced the intradermal test for identification of allergen sensitization and the protein nitrogen unit for standardization of allergen extracts. His contemporary, Dr Arthur F. Coca, who coined the term *atopy*, found that a serum factor (later identified as IgE) had unique properties that distinguished it from other types of antibodies. It was heat-labile and became fixed to cells in the skin, eliciting a wheal and flare response. Although it did not cross the placenta, it could be transferred through blood transfusion, causing a temporary sensitization in the recipient.

The 1930s and 1940s were characterized by studies of the immunopathophysiology of anaphylaxis in animal models, following in the tradition of Drs Paul J. Portier and Charles R. Richet's early 20th century landmark experiments describing and naming anaphylaxis in a dog model. In the 1930s, Dr Brett Ratner established a guinea pig model in which inhalation of antigen (horse dander), like injection of horse serum, could trigger anaphylaxis. He also studied the anaphylactogenic properties of milk, cereals, and other foods in this model. In 1944, Dr R. T. Fiske authored a paper entitled, "The Experimental Use of Ethylene Disulfonate (Allergosil Brand) in the Prevention of Anaphylaxis in Guinea Pigs." In addition to dogs and guinea pigs, animal models that dominated experimentation in anaphylaxis during these decades also involved mice, rabbits, and rhesus monkeys. This work presaged later studies in the rabbit by Dr Sheldon Cohen, and in the guinea pig by Drs Murray Dworetzky, Charles Code, and George Higgins.

The names of Drs Sidney Friedlaender, Alex Friedlaender, and Saul Malkiel figure prominently in the literature of the 1940s and 1950s by virtue of their use of these animal models. They began to unravel the secrets of anaphylaxis, performed studies of the effect of modulators such as adrenocorticotrophic hormone, and were the first to study effects of β -adrenergic blockade on anaphylaxis.

In the 1950s and 1960s, investigators began to investigate human reactions to penicillin and to allergen skin testing and immunotherapy. Dr Sam Feinberg published one of the earliest studies attempting to identify penicillin allergy by skin testing. Drs Bret Ratner and Oscar Swineford, Jr, vividly described anaphylactic events occurring during skin testing.

During this time, Dr Carl A. Dragstedt, in a long-term association with Dr Sam Feinberg, began to unravel the roles of various mediators in anaphylactic events. In a review of the mediators of anaphylaxis, studying guinea pigs and dogs, they came to the prescient conclusion that histamine was a major mediator, but that “there is a certain amount of evidence, not yet complete, indicating that other substances besides histamine and heparin may be concerned in some of the phenomena.” Citing evidence that “while Dr. Schild has shown that the addition of antigen to the bath, in which the uterus of a sensitized guinea pig is suspended, leads to the liberation of histamine from the uterus, he has also shown that the uterine contractions so produced are not wholly accounted for by the histamine released... Drs. Charles Kellaway and Everton Trethewie have presented evidence that another smooth muscle stimulating substance of a lysocytin-like nature may be partially concerned in this effect.” This exciting work was followed in the 1970s by the successful endeavors of Drs K. Frank Austen and Charlie Parker with regard to identification of the nature of slow reacting substance of anaphylaxis, and description of the biological properties of leukotrienes.

Dr George Mikulich was perhaps the first to identify the manifestations of anaphylaxis on the heart using a rabbit model, recording electrocardiographic changes. The validity of his findings has been confirmed multiple times over the years.

Throughout the early years, there were frequent articles on antihistamines. Detailed studies were conducted by Drs Sam Feinberg, Rudolf Mayer, Samuel J. Levin, George Waldbott, Sidney Friedlaender, Carl E. Arbesman, George Koepf, and Alfred Lenzner. One of attributes of this new class of medications they described was the beneficial effect of antihistamines on the urticarial manifestations of anaphylaxis.

In the mid-1950s, Drs Kenneth P. Mathews, Robert Lovell, Warren Forsythe, and John Sheldon described the preventive effect of chlorpheniramine on the urticarial manifestation of anaphylaxis, but no other manifestations. They evaluated every student who was prescribed penicillin at the University of Michigan Student Health Service and found that chlorpheniramine failed to produce a “significant effect on the incidence of delayed or severe penicillin reactions, although there was a reduction of early reactions, particularly those of an urticarial type.”

One of the most important observations during these years was made by Dr Mary Loveless and was beautifully summarized in a 1957 article in *The Journal of Allergy* recording discussions, chaired by Dr William Sherman, of a group of allergists on mechanisms of the allergic response. In this article, Dr Loveless commented, “I think that transfusion experiments (with sera containing blocking antibody) which, unfortunately, I did not publish, show quite conclusively that transfusion of large amounts of

blocking serum from a normal subject who had been immunized to pollen were promptly protective against hay fever, and this lasted about the expected time—10 days or so.” What a wonderful harbinger of later experiments performed by Dr Larry Lichtenstein and associates detailing the efficacy of IgG “blocking antibody” preventing anaphylactic reactions to *Hymenoptera* stings. In that same volume, Dr Loveless published an article analyzing the difference between blocking antibody and “reaginic antibody” using “electrophoresis-convection” for the fractionation and refractionation of proteins. It was perhaps the first observation that “sensitizing activity migrates electrophoretically with the β -globulins of serum, blocking antibody with the gammaglobulins.”

In the 1950s, Dr Zoltan Ovary developed the passive cutaneous anaphylaxis test for quantitation of anaphylactic antibodies. In the same decade, Drs Francis Lowell, William Franklin, and Irving Schiller made important, detailed observations on the clinical manifestations of anaphylaxis. In a particularly interesting quote from this article, they wrote, “an unexpected finding was the lysis of clot formed in blood after the induced reactions (fibrinolysis) in three instances.” This was perhaps the first observation of the fact that mediators from mast cells can activate other phlogistic pathways during anaphylactic events, later documented in exquisite detail by the Johns Hopkins group studying patients who received insect stings under observation in intensive care unit conditions. Dr Allen Kaplan, who was a coinvestigator in these studies, clearly showed that the contact system was activated during these events, along with clotting, complement, and clot lysis.

There were several studies of penicillin allergy in the late 1950s and early 1960s. Drs Robert Reisman, Noel Rose, Ernest Witebsky, and Carl Arbesman recorded one of the first successful desensitizations to penicillin along with observations regarding the immunologic response to desensitization. Decades later, their observation that “there is great need for better immunologic testing in the field of drug allergy is unfortunately still true. The use of breakdown products of penicillin may shed light in this direction.” A few years later, Drs Bernard Levine and Alain deWeck found that patients with systemic reactions to penicillin demonstrated different skin sensitivities to various penicillin preparations, including the major and minor antigenic determinants which they had identified.

Drs Bernard Levine, David Zolov, and Anthony Redmond began their hallmark work on penicillin allergy, reporting data on skin testing with penicilloyl-specific skin sensitizing antibodies. They noted the protective effect of IgG blocking antibodies, and in studying desensitization, they found that in some instances, skin test reactivity to penicillin was totally lost. They called this phenomenon “true desensitization,” and distinguished the mechanism of protection in these patients from those protected by the later production of blocking antibody.

In 1964, in a landmark publication in *The New England Journal of Medicine*, Dr Lewis P. James and Dr K. Frank Austen reported 6 fatal cases of anaphylaxis. Triggers included penicillin, allergen immunotherapy, and bee venom. They found that acute laryngeal edema or pulmonary "emphysema," or both, accounted for the fatal outcome in 5 of the 6 patients, and concluded that upper respiratory tract edema represented an important species characteristic in human anaphylaxis.

One of the earliest documentations of the adverse effects of β -blockers in anaphylactic events was conducted by Drs Robert Townley and Andor Szentivanyi, who published an article entitled, "Sensitization to Anaphylaxis and Some of Its Pharmacologic Mediators by Blockade of the Beta-Adrenergic Receptors." By using a mouse model, they demonstrated that β -blockade was associated with an adverse response and concluded that the activity of β -blockers "is due to their ability to inhibit the beta-pharmacologic actions of the adrenergic neural transmitters." The full clinical impact of these findings was subsequently described by Dr Robert Jacobs and Dr John H. Toogood.

Also in the 1950s and 1960s, work regarding *Hymenoptera* sensitization began to blossom in several centers. Drs Carl Arbesman and Robert Reisman began a long campaign to elucidate the mechanisms underlying anaphylaxis to *Hymenoptera* stings and improve the immunotherapy process. In 1956, Dr Mary Loveless pioneered the use of pure wasp venom for immunotherapy in patients with anaphylaxis to wasps. At this time as well, the Insect Sting Committee of the Academy, led by Dr James Henry Barnard, began to report on the epidemiology of insect sting reactions. In 1967, he published an account of 50 autopsies conducted on patients dying from insect sting anaphylaxis. He reported that respiratory tract angioedema was associated with most of the fatalities, thus confirming the earlier report of Drs James and Austen.

Perhaps one of the most salient observations of the late 1960s was made by Drs Howard Schwartz and Bertram Kahn, who were among the earliest investigators to observe that insect sting hypersensitivity frequently occurs in nonatopic individuals, and concluded that atopy "is not a prerequisite for the development of other types of anaphylactic hypersensitivity."

MORE RECENT TIMES

It is not easy to define an era of allergy research, which is a continuum. However, one could certainly argue that the discovery of IgE by Drs Teruko and Kimishige Ishizaka, and Dr Gunnar Johanssen (with Dr Hans Bennich), in the late 1960s ushered in a new era of research into anaphylaxis and other allergic diseases. Simultaneously, there was a growth of

academic centers focusing on research and training in allergy-immunology, thus increasing the number of well trained allergists-immunologists. With these changes came concerted efforts to unravel the mechanisms underlying anaphylactic events and simultaneously improve the care of patients with anaphylaxis.

In the early 1970s, Drs Jerry Dolovich, Fred Hargreave, Gerry Gleich, Graham Solley, and others first drew attention to the late-phase allergic reaction. The concept that there could be a late-phase reaction in anaphylaxis was introduced by Drs V. T. Popa and S. A. Lerner, and was later studied by Drs T. J. Sullivan, B. J. Stark, Hugh Sampson, Louis Mendelson, James Rosen, D. M. Douglas, E. Sukenick, W. P. Andrade, and J. S. Brown.

Many advances in anaphylaxis research have focused on investigations directed at the various causes of anaphylactic events. Without doubt, some of our members' greatest contributions have been in the area of *Hymenoptera*-induced anaphylactic events. As noted, Drs Carl Arbesman and Robert Reisman pioneered work in this area and later documented the role of IgE in these events, the natural history of *Hymenoptera* allergy, the significance of local reactions, and the efficacy of immunotherapy.

As early as 1973, Dr Robert Reisman, then Chair of the Academy's Insect Sting Committee, wrote an editorial in *The Journal of Allergy* in which he cast doubt on the efficacy of whole body extract therapy. At Johns Hopkins University, a group led by Dr Larry Lichtenstein, and including Drs Anne Kagey-Sobotka, Martin D. Valentine, David Golden, Phil Norman, Ken Schuberth, J. Hunt, A. K. Benton, F. J. Amodio, Bradley Chipps, and others, completely revolutionized the way we deal with immunotherapy for *Hymenoptera* venom reactions. Who would have thought, based upon the previous observations of the value of whole-body extract immunotherapy, that this treatment was ineffective? It was the Johns Hopkins group that, in an iconoclastic manner, shattered our passionately held false knowledge. They conclusively demonstrated that pure venom therapy, and not whole-body extracts, was the only efficacious material for desensitization. This work continues to the present at Johns Hopkins under the direction of Dr David Golden and others. Our knowledge of anaphylaxis to insect stings has also been furthered by the work of Drs Ulrich Muller, James Day, Jacob Pinnas, Richard DeShazo, Jorreg Kleine-Tebbe, and others.

In 1974, Dr Richard Lockey published his first studies on fire ant sting allergy, a series of 6 detailed case reports. Later, his work on anaphylaxis and adverse reactions to allergen skin testing and allergen immunotherapy altered our approach to immunotherapy, and recommendations based on his careful documentation of adverse reactions have helped to reduce morbidity and mortality caused by skin testing and immunotherapy. In subsequent decades, Drs Richard deShazo, Donald Hoffman, Sami Bahna, Ted Freeman, and

others also contributed to the diagnosis and prevention of anaphylaxis from fire ant stings.

During these 3 or 4 decades, work on anaphylaxis as a result of diagnostic agents has flourished. One of the paradigms for this involved observations on reactions to radiocontrast material. Several different investigators, initially centered at Northwestern University and the University of Pennsylvania, began to publish a series of practical approaches to patients subject to radiocontrast material reactions who had to undergo a subsequent procedure using these materials. The pretreatment regimen that resulted from these observations, including prednisone, diphenhydramine, and ephedrine, has subsequently been used successfully in many settings. Many physicians contributed to this pretreatment protocol, but the initial leadership came from Drs Roy Patterson and Burton Zweiman. Others who have participated in the multiple studies in this area include Drs E. A. Hildreth, Michael Schatz, Ronald Simon, Joseph F. Kelly, Paul Greenberger, Michael Kaliner, Johannes Ring, Donald Stevenson, Allan Kaplan, Robert Orange, David Lang, M. W. Yocum, Dennis Ledford, Rebecca Gruchalla, Roland Solensky, Tim Sullivan, and Phil Lieberman.

Northwestern University investigators Drs Leslie Grammer, Paul Greenberger, and others have performed drug allergy studies and developed meticulous detailed treatment protocols for drug allergies. This work has been continued in St Louis by Dr Mark Dykewicz, adding to our knowledge of reactions to numerous drugs including streptokinase, protamine, folic acid in vitamin supplements, and insulin. Dr Leonard Bernstein also contributed to our understanding of drug reactions through his work with chymopapain. The contributions of the Scripps Group, Drs Donald Stevenson, Ronald Simon, David Mathison, and others, to our knowledge of drug reactions to aspirin and other nonsteroidal anti-inflammatory drugs have greatly improved the care of patients. Dr Dennis Ledford's scholarly efforts in defining the contributing factors toward anaphylactic events during general anesthesia have contributed greatly to our approach to the patient with this disorder. Our clinical approach to the patient who is subject to penicillin anaphylaxis has been greatly enhanced by the work of Drs Paul VanArsdel, Warren Bierman, Richard Warrington, Louis Mendelson, C. Ressler, James P. Rosen, and others. Our management of local anesthetic reactions has been illuminated by the efforts of Drs Michael Schatz, Roy Patterson, Rick DeShazo, Daniel Vervloet, and others.

Another major area of investigation has been food allergy. Through the innovations of multiple investigators, many of whom are stalwarts of the Academy, have come great advances in our knowledge of the epidemiology, clinical manifestations, allergen characterization, and therapy of food-induced anaphylaxis. Although patients with anaphylaxis caused by food were described sporadically in the early years,

symptoms were often attributed to poisoning rather than to an immunological reaction. The first case series of patients with anaphylaxis triggered by ingestants, with associated descriptions of immunologic mechanisms, was published by Drs Thomas Golbert, Roy Patterson, and Jacob Pruzansky in *The Journal of Allergy* in 1969. Dr Charles May was perhaps the first to demonstrate "an increased spontaneous release of histamine in individuals subject to 'anaphylaxis'" to food. Dr May, along with Dr Allan Bock, pioneered the use of the double-blind, placebo-controlled food challenge. This early work paved the way for the use of this technique by several investigators whose observations on anaphylaxis to ingestants have filled the literature and have drastically changed our approach to food allergy. The contributors to this body of knowledge are multiple, and perhaps too numerous to name, but the AAAAI leaders in this area include Drs Hugh Sampson, John Anderson, Kristen Beyer, Carsten Bindslev-Jensen, Allan Bock, Wesley Burks, Phillippe Eigenmann, Terry Furlong, John James, Stacie Jones, Dean Metcalfe, Anne Munoz-Furlong, Scott Sicherer, Steve Taylor, Peter Vadas, Robert Wood, John Yunginger, J. Flabbee, D. A. Moneret-Vautrin, G. Kanny, M. Morisset, L. Parisot, Bruce Prenner, Mario Sanchez-Borges, Constantine Falliers, and Michael Glovsky. The last decade has seen great advances in the translation of these research efforts to improvements in patient care. The future holds considerable promise with regard to development of immunotherapeutic agents.

One of the most enigmatic, yet revolutionary, ideas regarding anaphylaxis came from Dr Roy Patterson and associates, who introduced the concept that anaphylaxis episodes could be idiopathic—that is, could occur without exposure to an allergen or other obvious trigger factor. Since the first report from Northwestern University in 1978, many investigators have contributed to the literature on idiopathic anaphylaxis, including Drs Paul Greenberger, Stephen Kemp, Mark Dykewicz, Lesley Grammer, Johannes Ring, Ulf Darsow, and others.

Similarly, the concept that anaphylaxis could be a result of physical factors such as exercise and cold, as first described by Dr Al Sheffer, was revolutionary when first introduced. Several others have contributed to the literature on exercise-induced anaphylaxis. They include Drs Richard Horan, Larry DuBuske, Jordan Fink, J. M. Kidd, A. G. Sosman, A. L. Schocket, R. M. Marletts, K. Frank Austen, J. P. Wade, Alan A. Wanderer, H. Hoffman, and others.

An unexpected development was the epidemic of allergic reactions to natural rubber latex. Beginning in 1989, Academy members led the work on latex allergy through the efforts of Drs Dennis Ownby, John Yunginger, Jordan Fink, Kevin Kelly, Jay Slater, Donald Beezhold, and Gordon Sussman. Their research serves as a paradigm of both epidemiologic and mechanistic studies designed to eliminate a public health threat. They have contributed to a marked

reduction in latex-induced anaphylactic events in healthcare facilities and elsewhere.

Because the mast cell has been key to our understanding of anaphylaxis, one could not refer to advances in this area without mentioning the names of people who have contributed immeasurably to our knowledge of the mast cell and its mediators, and also to the phenomenon of anaphylaxis occurring during systemic mastocytosis. A great deal of our knowledge in this area has sprung from the "Brigham" via the efforts of Dr K. Frank Austen and all of the people who have trained under his tutelage, including Drs Dean Metcalfe, Robert Orange, and Steve Wasserman. Through the work of Dr Larry Schwartz and Dr John Yunginger, serum tryptase measurements are now used to support the diagnosis of anaphylaxis. We have also learned a great deal about mast cell biology from the work of Dr Richard Stevens.

The treatment of anaphylaxis has changed little since the introduction of epinephrine in the early 20th century and the development of antihistamines in the mid-20th century. Academy members have conducted innovative experiments with these medications that have led to improvements in the treatment of anaphylaxis. Dr Michael Kaliner, along with investigators at Walter Reed and the National Institutes of Health including Drs J. H. Shelhammer and E. A. Ottesen, documented the importance of the H₂-receptor in mediating the symptoms produced by histamine and developed the rationale for the use of H₂-antagonists in the prevention and treatment of the acute event.

Although epinephrine is the cornerstone of treatment in anaphylaxis, it has never been optimally studied in this disease. During the past decade, in a coordinated series of investigations defined by their elegant simplicity, Dr Estelle Simons has led a team of colleagues in experiments designed to answer practical questions about the use of epinephrine in anaphylaxis, particularly in a community setting in which no assistance from healthcare professionals is available.

Characterization of patients presenting to emergency departments with anaphylaxis, and their treatment (or lack of it), has been recently performed by Dr Carlos Camargo, Dr Ray Mullins, and others.

The exact incidence and epidemiology of anaphylaxis is still unknown, but Academy members have contributed immeasurably to the body of knowledge in this area. Drs J. S. Klein, J. H. Butterfield, Stephen Kemp, David Kahn, Bruce Wolfe, and M. W. Yocum have made contributions through chart reviews.

Animal models of anaphylaxis continue to be instructive in the elucidation of pathophysiologic mechanisms. In recent decades, contributors in this area have included Drs Fred Finkelman, Marc Rothenberg, Eric Brandt, Hans Oettgen, Xiu-Min Li, Suzanne Teuber, and Oscar L. Frick.

CONCLUSION

From the foregoing, it is obvious that many AAAAI members and their colleagues have contributed greatly to basic science, transitional science, and clinical science knowledge in anaphylaxis. This review should be considered a first step in identifying and collating the contributions of AAAAI members around the world to this area during the past 83 years. As we expand this material in the future, the authors welcome input from colleagues about additional AAAAI members' contributions.

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Editor's note: References 2 through 4 are historical sources not specifically related to any particular place in the article.

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