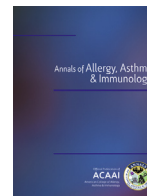




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Perspective

Historical perspectives of allergy and immunology and allergen immunotherapy

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ARTICLE INFO

Article history:

Received for publication September 11, 2014.

Received in revised form October 2, 2014.

Accepted for publication October 3, 2014.

Early Interest in the Specialty

During my youth, I had my first encounter with the specialty of allergy while assisting my physician-father, an allergist/immunologist, in preparing allergen extracts from ragweed pollen and house dust. These extracts were used for skin testing and subcutaneous immunotherapy (SCIT) in his clinical practice in Lancaster, Pennsylvania. It was a common practice before commercial extracts were universally available in the United States. My father was initially trained as a family practitioner and later, after the World War II, took an apprenticeship in allergy/immunology at the University of Pennsylvania, Philadelphia, Pennsylvania. Thereafter, he devoted his entire life to the field. He was the founding father of the Pennsylvania Allergy & Asthma Association and an active member of both the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology (AAAAI) and usually had an abstract or two to present at their annual meetings. I vividly remember attending these meetings with my 2 brothers: my older brother, Stephen Daniel Lockey, a practicing allergist/immunologist in Lancaster, Pennsylvania, and my younger brother, James Edward Lockey, a pulmonary/occupational physician and academician at the University of Cincinnati, Ohio. Training in the specialty was not formalized until 1971.¹ Figure 1 is a picture of my late father and his charge nurse, Ms. Sarah Landis, taken in the early 1950s.

While attending Haverford College, Haverford, Pennsylvania, I had the privilege of participating in immunologic research in a basic research laboratory, where I became fascinated with the world of immunology, an area of special interest to 2 of my professors, Irving Finger, PhD, and Mel Santer, PhD. I vividly remember plating out Petri plates with agar gel, cutting and aspirating the wells, and then applying antigen and serum containing antibodies prepared in rabbits for Ouchterlony double-diffusion studies. Likewise, similar studies were performed in capillary tubes. I also remember how

disappointed I was when my roommate's name was included on an abstract and, ultimately, on a published article on the research we were doing, whereas mine was not. Dr Finger informed me that in order to have your name included on an abstract or paper, one had to contribute to the research, not just do the technical work.

After admission to Temple University Medical School, Philadelphia, Pennsylvania, in 1961, I spent the first several years learning a second language and the complexity of medical science. Lectures about allergy/immunology were included in the curriculum. I was fascinated to once again observe and now understand skin test reactions, both immediate and delayed, which I had seen in my father's office years before, as well as to understand the importance of a conjunctival challenge study. Two professors, Drs Louis Tuft and George Blumstein, were instrumental in continuing my interest in allergy and immunology. My first research project while a senior medical student and during my internship at Temple was mentored by the late Dr Felix Cortes, a pulmonologist at Temple and later chief of medicine at Ponce Medical School, Puerto Rico. He involved me in a project to study blood gases and cardiac output in patients with acute asthma as they reported to the emergency department or when they were admitted to the hospital. The standard of care in 1965 and 1966 was to prescribe meperidine and/or a barbiturate as part of emergency treatment.² Both these medications were known to diminish respiratory drive and thus increase the risk for hypoxia. The study on blood gases found that severe blood gas abnormalities existed in many of these patients, some of whom had respiratory alkalosis and others of whom were hypoxemic and acidotic. These blood gas abnormalities were extremely impressive to me because of the inappropriate and widely accepted use of such medications in patients who were in severe respiratory distress to allegedly relieve their anxiety. Of course, the anxiety was not the problem, it was their asthma. When this knowledge became known to the medical community, administering these medications to such patients was quickly discontinued.

Training in Internal Medicine and Allergy and Immunology

After my training in internal medicine at the University of Michigan, Ann Arbor, I spent 2 additional years in allergy and

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Disclosures: Author has nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2014.10.003>

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Figure 1. My late father, Stephen D. Lockey, MD, with his charge nurse, Ms Sarah Landis, in approximately 1950.

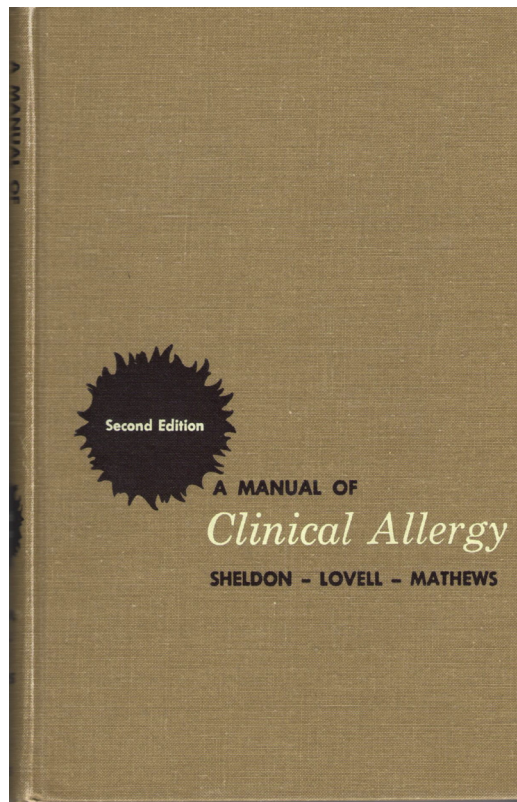


Figure 2. *A Manual of Clinical Allergy*, 1967 edition.

immunology at this same institution. The contents of the training were primarily based on clinical impressions rather than evidence-based medicine. The book entitled *A Manual of Clinical Allergy*, edited by Sheldon, Lovell, and Mathews, was used for training (Fig 2). It was a 550-page book written by the faculty, including the late Drs John M. Sheldon, Robert G. Lovell, Kenneth P. Mathews, and James A. McLean and Drs William R. Solomon and Neal A. Vanselow.³ Contrast this book with the eighth edition of Middleton's *Allergy: Principles and Practice*, which is 1896 pages.⁴ The following excerpts from chapter 6, entitled "Specific Therapy: Avoidance and Hyposensitization," are of great interest.⁵

- "However, enough problems have been solved to permit one to say that hyposensitization with ragweed pollen extract, grass pollen extract and, possibly house dust extract has been carried out under reasonably well controlled conditions, and in some of these studies a significant therapeutic effect was demonstrated."
- "The selection of [sic] allergens [sic] is made on the basis of the history with confirmatory evidence from skin, ophthalmic, or inhalation tests. Since multiple sensitization is commonplace, one frequently has occasion to treat patients with mixtures of antigens."
- "Injections of allergens should be carried out only in a physician's office or in some comparable place where professional personnel and drugs are available to treat any reactions which might occur."
- "Excessively large local swellings should be avoided because they are uncomfortable and because they may presage development of more severe constitutional symptoms."
- "The mild type of constitutional reaction may be manifested by a repetition of the patient's symptoms for which he is receiving hyposensitization, e.g., rhinorrhea, nasal stuffiness, itching of the nose or eyes, sneezing, cough, wheezing, or conjunctival redness."

Death most likely results from respiratory tract obstruction at either the bronchiolar or laryngeal-tracheal level, or the patient expires from shock."

- "Unfortunately, there is a dearth of systematic long-term studies of patients which have been recorded during and after hyposensitization therapy. Hyposensitization often is terminated when the patient has gone through three seasons with few symptoms."
- "Some treatment failures can be explained by incorrect diagnosis, the use of improper or impotent extracts, or inadequate dosage."

These clinicians were astute in their thinking as indicated by these statements, most of which remain relevant to allergen immunotherapy to this day.

During training and while at the Rackham Graduate School of the University of Michigan, blood group antigens became my area of interest. Working in a basic laboratory, one became acutely aware of the complexity of the immune system and the fact that the specialty of allergy and immunology was just in its infancy. During my training, aspirin-exacerbated asthma was also an area of interest, and, at the urging of Neil Vanselow, MD, one of my professors, we were able to demonstrate a genetic link for this syndrome. Of great interest to me was that the monozygotic twin sisters in this study developed different phenotypes of asthma, one allergic and the other aspirin-exacerbated asthma.⁶ I was fascinated by the fact that "experiments of nature," as so often quoted by the late Dr Robert A. Good, the father of clinical immunology of the 20th century, when referring to various primary and secondary immunodeficiency diseases, could result in translational research to benefit medical science.⁷

Thereafter, in 1970, I joined the US Air Force (USAF) and served as an internist and allergist/immunologist at Carswell Air Force Base Hospital in Fort Worth, Texas. Young active-duty service members and their families, as well as many retirees, were the

patients cared for at the hospital clinic. This experience confirmed my impression that many of the concepts we followed in medicine and, in particular, in our specialty, including SCIT, were based on clinical impressions and few well-designed scientific-based studies. During this time, I worked with Dr Raymond Zeiss, and together we performed clinical studies with patients with aspirin-exacerbated asthma and found that desensitization to aspirin was possible. One patient with this disease, who had severe asthma secondary to the ingestion of aspirin, was able to tolerate aspirin for up to 3 to 5 days after an initial aspirin-induced exacerbation.⁸ This clinical paradox fascinated us and was instrumental in both of us entering academic medicine. Dr Zeiss became a faculty member and, ultimately, a professor at Northwestern University, Chicago, Illinois, and I became a founding faculty member at the new College of Medicine, University of South Florida, Tampa.

Just think, the main treatment for asthma in the early 1970s was a combination of some or all of the following medications: aminophylline, ephedrine, hydroxyzine hydrochloride, isoproterenol, phenobarbital, and others.^{2,9} Inhaled isoproterenol was one of the mainstays for acute asthma. Patients died in certain countries of the world of the overuse of this medication.^{10,11} Transporting asthmatic patients in acute distress to the operating room to give them general anesthesia and then intubating them was not an unusual occurrence. Epinephrine (1:1,000 vol/vol) was the mainstay of treatment (ie, 0.3–1.0 mg every 30 minutes, repeated as necessary).² Systemic glucocorticosteroids also were available. Although they were known as wonder drugs, for years, there was some reluctance to use them as they are used today because of a lack of knowledge about how they should be optimally prescribed and fear of possible serious adverse effects associated with their use. Theophylline toxicity also was a common occurrence.¹² Hospitalization and intubation to assisted ventilation were not an unusual chain of events for patients with severe asthma. The water-sealed Jones spirometer and the piston-driven Emerson ventilator were the standards of care. I vividly remember “Ambu bagging” patients with severe respiratory distress from asthma in an ambulance as they were transported from Carswell Air Force Base, Fort Worth, Texas, to Parkland Memorial Hospital, Dallas, Texas, the hospital where President John F. Kennedy was transported when he was assassinated. These piston-driven ventilators became available during my second year at Carswell Air Force Base, and transportation to another hospital for such cases was no longer necessary.

In 1973, after my 2-year stint as a major in the US Air Force, I joined the late Dr Samuel C. Bukantz, my mentor and founder of the Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida College of Medicine and James A. Haley Veterans’ Hospital, Tampa, Florida. We had many conversations about the specialty and, in particular, about SCIT and the lack of adequate science to confirm its efficacy and provide information for its optimal use. Both of us thought it was an important form of therapy, in particular, because of the lack of more effective pharmacologic treatment in use at that time. Evidence also was lacking not only for efficacy but also for safety. Systemic allergic reactions were very common, some of which were severe and occasionally caused death.

Evolution of Allergen Immunotherapy

Several years before moving to Florida, I had already joined the American Academy of Allergy, now the AAAAI, and became a member of the Committee on Insects. In 1979, the work by Hunt et al¹³ from Johns Hopkins University, Baltimore, Maryland, indicated that Hymenoptera venom was effective, whereas whole-body extract immunotherapy was not, to treat venom hypersensitivity. This had been previously illustrated by the late Dr Mary Loveless in

noncontrolled venom studies.¹⁴ Paul Turkeltaub, MD, a staff member of the Food and Drug Administration (FDA), urged the committee to undertake phase 4 Hymenoptera venom studies. These were organized under the auspices of the AAAAI Committee on Insects to determine whether venom skin testing and immunotherapy was safe and effective, in particular, when used in numerous patients by many North American practicing clinicians. The research resulted in several publications indicating that skin testing and SCIT with standardized venoms were safe as long as the appropriate guidelines, as recommended by the FDA, were followed.^{15–17} Likewise, there were no major long-term adverse effects from the use of these venoms.

The use of standardized venom vaccines for venom immunotherapy to treat Hymenoptera hypersensitivity was a hallmark for the specialty because (1) it demonstrated that venoms versus whole-body extracts were effective; (2) standardized venom extracts that were safe and effective became available for skin testing and SCIT; and (3) immunologic changes associated with such therapy correlated to some extent with efficacy. No deaths, even to this day, have been reported from venom therapy.

About this same time, the late Dr John Salvaggio from Tulane University, New Orleans, became the first editor of the *Journal of the American Medical Association Primer on Allergic and Immunologic Diseases*, published in 1982¹⁸ (Fig 3). The 13-page chapter entitled “Immunotherapy–Immunomodulation,” written by the late Dr Roy Patterson and Dr Phil Norman and the late Dr Thomas Van Metre, devoted only 2 pages to SCIT.¹⁹ This is one of the first major international publications about this subject published in many languages and read by physicians throughout the world. The primer also was a landmark publication for the specialty as a 174-page treatise on the specialty of allergy and immunology written by more than 100 physicians and scientists, providing national and international recognition to the specialty.

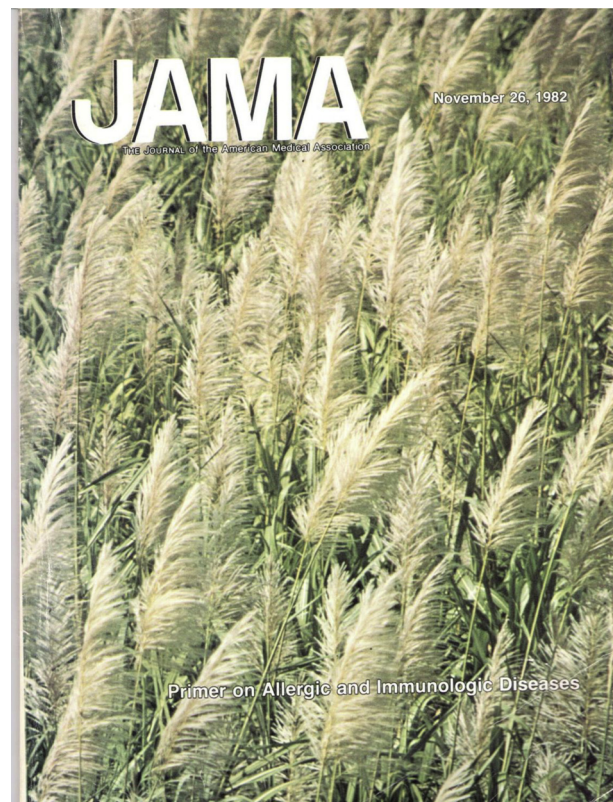


Figure 3. First edition (1982) of the *JAMA Primer on Allergic and Immunologic Diseases* edited by the late John Salvaggio, MD.

To give you an idea of the evolution that was occurring at that time, in the second edition of the primer, which I had the privilege of editing with the late Dr Samuel C. Bukantz, chapter 4, written by Drs Peter S. Creticos and Phil S. Norman, was entirely devoted to “Immunotherapy With Allergens.”²⁰ The acceptance of SCIT as a scientifically based treatment modality was becoming more widespread. Two additional primers were published subsequently: the first in 1992, edited by Drs Richard D. deShazo and David L. Smith, and the last, in 1997, edited by Dr James R. Baker.^{21,22} All primers were published in many languages and distributed to physicians throughout the world. The specialty of allergy and immunology had arrived!

Deaths from SCIT, especially in the latter half of the 20th century, were also being discussed and reported to various regulatory institutions in the United States and other countries. This resulted in a second major undertaking, once again encouraged by Dr Paul Turkeltaub and the FDA under the auspices of the Academy's Committee on Immunotherapy. A survey of allergists/immunologists who practiced in North America was devised to determine the number of fatalities associated with SCIT. This survey, which began in 1983, continues to this day. The first large epidemiologic article on this subject was published in the *Journal of Allergy and Clinical Immunology* and reported 46 deaths, 6 from skin testing and 40 from SCIT.²³ Slightly earlier, a 1-page report from Great Britain's Committee on Safety reported on 26 fatalities most likely associated with modified extracts vs aqueous extracts, the latter of which were primarily being used for SCIT in the United States.²⁴

These reports were sentinel because they indicated that SCIT was not entirely safe. This was followed by several similar reports and gave more impetus to the FDA to standardize allergen vaccines and better regulate their manufacturing process and the means by which they are used by physicians in the care of allergic patients.^{25–27} About the same time, the Committee on Immunotherapy began to develop SCIT guidelines, which today have evolved into detailed practice parameters, not only in the United States but also in other parts of the world. Dr Peter Creticos and I, along with Drs Bukantz, Dennis Ownby, Jay Portnoy, Turkeltaub, and Richard Weber, developed the first such parameters on SCIT entitled *Immunotherapy: A Practical Guide to Current Procedures*²⁸ (Fig 4). It incorporated chapters on aerobiology, skin testing, allergen extract potency and stability, standardized extracts in practice, efficacy parameters, indications and contraindications of allergen immunotherapy, forms used for skin testing and immunotherapy, and adverse effects and fatalities associated with immunotherapy and skin testing. Today, practice parameters on SCIT are updated approximately every 5 years in the United States and are more extensive, covering every aspect of the appropriate manner by which SCIT should be prescribed and administered.²⁹ Only one death in the United States has been reported associated with SCIT from 2008 to 2012.²⁷ I like to think that the decrease in the number of fatalities associated with SCIT is a result, at least in part, of the dedication of so many physicians and scientists to improve the safety of this form of therapy.

New Science and Forms of Allergen Immunotherapy

During the 1990s, additional studies were being published that indicated that SCIT was indeed an effective form of therapy. The immunologic changes associated with such therapy were being elucidated. Optimal doses were defined with more information published about how SCIT should be appropriately administered. Many physicians and scientists throughout the world now have a great interest in this form of therapy and continue to contribute to the knowledge about it and to devise safer and equally or more effective forms of allergen immunotherapy.³⁰

As the international exchange of information became more the rule rather than the exception, I had the great fortune of getting to

know Dr Jean Bousquet. Together, we repeatedly discussed the possibility of soliciting the assistance of the World Health Organization (WHO) to issue a position statement on allergen immunotherapy. A committee was formed, chaired by Dr Jean Bousquet, Dr Hans-Jørgen Malling, and myself. With 19 international colleagues, during a period of a year or so, a document entitled “WHO Position Paper: Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases” was constructed and distributed throughout the world³¹ (Fig 5). This scientific document, for the first time, placed allergen immunotherapy on the global map. Of interest, sublingual immunotherapy (SLIT) to treat allergic rhinoconjunctivitis was recommended for the first time.

Since 1998, SLIT has become a reinvented form of immunotherapy and is now an accepted form of immunotherapy throughout the world. SCIT had been used in the United States and elsewhere for many years; however, use of suboptimal doses was found not to be effective.³² Just as optimal doses are necessary for the efficacy of SCIT, so too are optimal doses necessary for SLIT. Today, there are properly configured powered studies that prove that such therapy is effective and safer than SCIT.³³ Likewise, the immunologic changes associated with SCIT also have been found with SLIT.^{33,34} Many different investigators have played a role in investigating this new form of therapy. Two important documents published on this subject include the World Allergy Organization (WAO) article entitled “Sublingual Immunotherapy: WAO Position Paper 2009”³⁵ and the article entitled “Recommendations for Appropriate Sublingual Immunotherapy (SLIT) Clinical Trials.” The latter established standards for all future trials.³⁶

New forms of allergen immunotherapy are being investigated, including the use of the Toll-like receptor 4 and 8 agonists, omalizumab with SCIT, modified and recombinant vaccines, and peptide immunotherapy. Likewise, different methods of administering

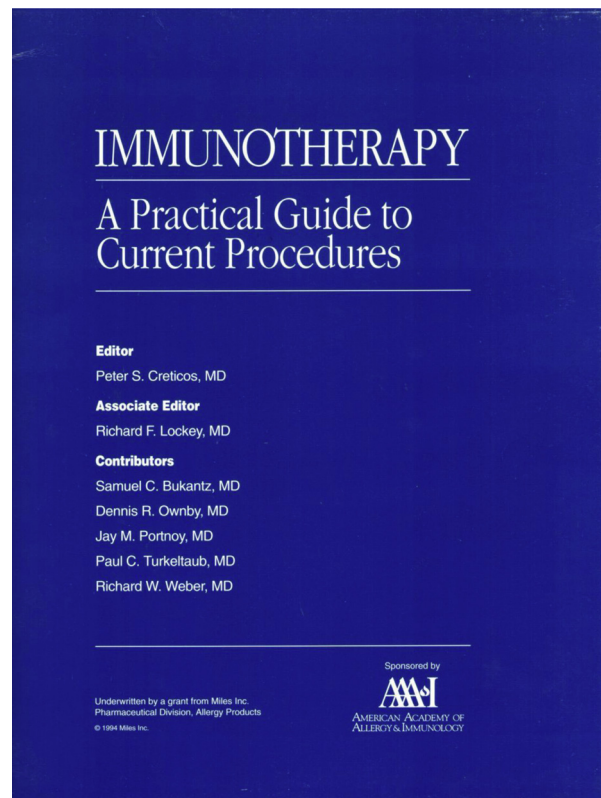


Figure 4. First practice parameters on allergen immunotherapy (1994).

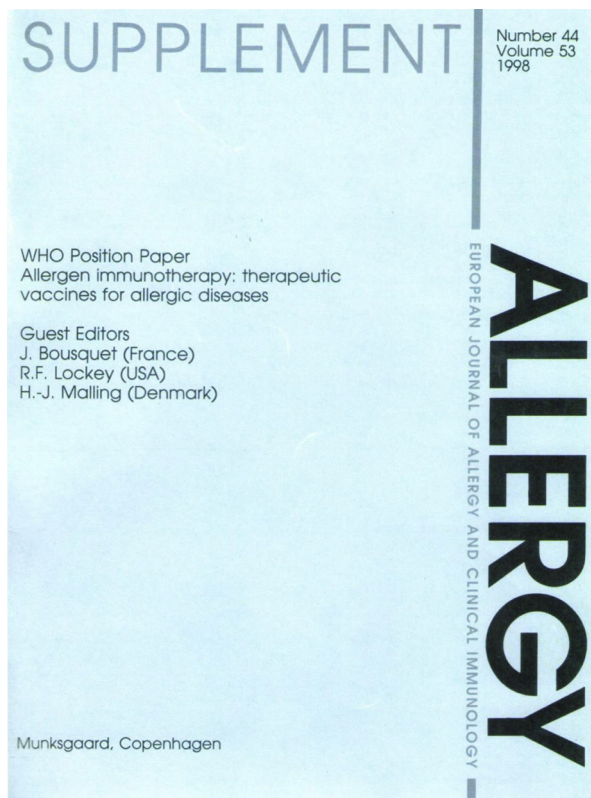


Figure 5. World Health Organization position paper on allergen immunotherapy (1998).

such therapy are under investigation and include intralymphatic, epicutaneous, oral, and intranasal allergen immunotherapy.³⁰

One additional comment is that I have had the privilege of coediting 5 editions of the book entitled *Allergen Immunotherapy*. The first edition, edited by Dr Bukantz and me, consists of 13 chapters, 26 authors, and 296 pages.³⁷ The newest edition, published in 2014 and edited by Drs Dennis K. Ledford and me, consists of 38 chapters, 75 authors, and 569 pages, illustrating how this form of therapy to treat allergic diseases has evolved.³⁸

Allergen immunotherapy has been used to treat allergic diseases for more than 100 years and will continue to be used not only to treat allergic diseases but also ultimately to prevent them. Various other forms of immunotherapy are also being used today to treat autoimmune and oncologic diseases. Vaccines of all kinds that augment the immune response or create immunologic tolerance will continue to be developed. Allergists/immunologists can be very proud of the tradition of using SCIT to modify the immune response and create tolerance to allergens that cause allergic diseases. Today, the term *immunotherapy* applies to not only allergen immunotherapy but also other forms of immunotherapy. Likewise, the term *allergen extract* largely has been replaced by the term *vaccine* because today vaccines are used to treat not only infectious diseases but also allergy, autoimmunity, and cancer.³¹

Conclusion

My observations and experiences with allergen immunotherapy transcend my entire life. This article is not just about my experiences with this form of therapy and some of the studies and initiatives in which I have had the privilege of participating but also about colleagues who have taught me and with whom I have had

the great privilege to work. All of them have helped to transform a specialty and a form of therapy that evolved clinically, with little science, to scientifically based treatment modalities.^{39,40} Many other advancements and forms of immunotherapy will be forthcoming not only to treat and prevent allergic diseases but also to treat and prevent other immunologically based diseases. The future is just beginning!

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