History of Immunotherapy: The First 100 Years

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KEYWORDS

- Allergen-specific immunotherapy • Allergic rhinitis
- Subcutaneous immunotherapy • Hypersensitivity

Allergen-specific immunotherapy (SIT) both defines and distinguishes the modern practice of clinical allergy and immunology as the 100th anniversary of this pioneering technique is celebrated. The ingenuity, resolve, and insight of the many forebears have led to this landmark achievement, and the progress that has been made after the original description of SIT in 1911 by Leonard Noon and John Freeman is remarkable. Despite the tremendous advancements made in therapeutics, pharmacology, and the basic science of allergy, SIT remains the only treatment modality that offers a potential cure for atopic diseases rather than simply an amelioration of symptoms. A historical perspective not only offers an opportunity to tell some of the fascinating stories that led to the conception of SIT but perhaps, more importantly, gives an occasion to recognize, remember, and honor those individuals who have contributed to its development (**Table 1**).

Although 1911 represents the beginning of the modern era of SIT, evidence supporting an understanding of the immune system and attempts to prevent or alter disease for the welfare of the patient dates to antiquity. Thucydides (circa 460–400 BC), an ancient Greek historian, observed that those patients fortunate enough to survive the plague were often protected against subsequent outbreaks, one of the first descriptions of immunity.[1] Mithadrates VI (circa 132–63 BC), king of Pontus and Armenia Minor, was so concerned about the possibility of poisoning that he developed a technique to protect against this danger in what may be considered the first example of oral tolerance, as recorded by Pliny the Elder: "By his unaided efforts he thought out the plan of drinking poison daily ... in order that sheer custom might render it

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Table 1
Landmark achievements in the history of allergen-SIT

Jenner[1]	First demonstration of vaccine principles	1798
Blackley[2]	First attempt at SIT via pollen application to abraded skin	1880
Richet and Portier[3]	Experimental description of anaphylaxis	1902
Noon and Freeman[4]	First successful pollen SIT trial	1911
Cooke[3,5]	Discovery of house dust as ubiquitous antigen; concept of blocking antibodies	1922, 1935
Lowell and Franklin[6]	First double-blind controlled SIT trial with purified extracts	1965
Ishizaka and Ishizaka[7]; Johansson et al[8]	Discovery of IgE	1967
Hunt et al[9]	Venom SIT vs whole-body extracts for Hymenoptera SIT	1978
Passalacqua et al[10]	Double-blind controlled SLIT trial for dust mite	1998
Durham et al[11,12]	Sustained efficacy of both SCIT and SLIT using grass pollen	1999, 2010

Abbreviations: IgE, immunoglobulin E; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

harmless."[3] Galen (AD 130–200), the celebrated Greek physician, observed that oral ingestion of snake venom avoids systemic toxicity; this insight may have inspired snake charmers of the era to swim in snake-infested waters in an attempt to ingest minute amounts of venom to afford protection against the occupational hazards of their profession.[1] By the 11th century, Chinese healers attempted the first efforts at active immunization against disease by instilling dried materials recovered from the pustules of patients with smallpox into the recipients' nostrils, known as variolation.[1]

Although variolation remained in practice for centuries, it was Edward Jenner, a rural English physician in the 18th century, who provided one of the keystone moments and ushered in the modern era of immunology. His acclaimed contribution is the first experimental demonstration of vaccination, in which he inoculated the fluid from cowpox lesions to protect against smallpox. This carefully documented experiment confirmed anecdotal reports from the time that milkmaids with cowpox were much less vulnerable to contracting smallpox and gave the procedure its name, vaccination, from the Latin word vaccinus (pertaining to a cow). Perhaps more relevant to practicing allergists/immunologists, however, he also provided the first description of cutaneous hypersensitivity on revaccination.[3] Although formal epicutaneous and intradermal allergen testing were still more than 100 years away, Jenner's astute observation that the degree of inflammation on reexposure to the cowpox inoculum reflected the relative immunity to smallpox showed remarkable insight. Although highly honored after his celebrated discovery, he remained in rural practice as a country doctor for the rest of his life.

A contemporary of Jenner from Great Britain, John Bostock, provided the first description of what is now termed seasonal allergic rhinoconjunctivitis. Dr Bostock's designation for the affliction in his original 1819 article was the lyrical and descriptive *catarrhus aestivus*, roughly translated as summer flow. He describes his own symptoms in this work in which he experienced ocular irritation, paroxysms of sneezing, and tightness of the chest (ie, "a feeling of want of room to receive the air necessary for respiration"), which began every summer in June.[3,13]

Although Bostock provided an important but limited descriptive contribution to allergic diseases, it is Dr Charles Blackley who substantially extended these observations to the cause and possible treatment of allergic rhinitis in his 1873 volume, *Experimental Researches on the Cause and Nature of Catarrhus Aestivus*. Dr Blackley, experimenting on himself, concluded that pollen was the responsible agent for his hay fever, the lay term that he preferred. He performed a series of experiments in which he instilled increasing amounts of pollen (initially rye grass but expanded to multiple other pollens) into his nostril and observed that "a profuse coryza came on in less than a minute after the application. In thirty minutes the nostril was completely occluded, so that it was quite impossible to pass any air through it."[2] Furthermore, he correlated the severity of his symptoms with the quantity of airborne pollen, having fabricated numerous devices of his own invention for the collection and quantification of atmospheric pollens. Out of desperation for a satisfactory treatment to alleviate his own suffering, he attempted medical management with a wide variety of agents, including quinine, arsenic, and belladonna, none with satisfactory results; however, he did acknowledge that one possibility for palliation would be a suitable change of locality. Finally, Dr Blackley made what can be regarded as the first investigational attempt at SIT by repeatedly applying pollen to his abraded skin in an effort to decrease local reactivity; however, no change was observed.[2]

After Blackley's seminal observations and innovations in the area of allergic rhinitis, there followed an important period of discovery into the concepts of antitoxin and the therapeutic use of antisera in passive immunization. Dr Henry Sewall, in 1887 at the University of Michigan, demonstrated in an animal model that protection against lethal envenomation from snakebites can be conferred by repeated inoculation of sublethal venom doses, giving rise to the concept of antitoxin.[1,14] By 1890, Shibasabura Kitasato and Emil von Behring, working collaboratively in the Robert Koch's laboratory in Berlin, developed tetanus and diphtheria antisera for therapeutic use.[3] However, it was not until 1897 that Paul Erlich had refined and standardized the production of diphtheria antitoxin that it found widespread commercial use.[1] Dr Erlich, of course, made a remarkable array of contributions not only in antitoxin research but also with the staining and identification of both mast cells and eosinophils, which would later be recognized to be fundamental to the pathogenesis of allergic diseases. At the dawn of the 20th century, several further attempts in passive immunization and experiments in anaphylaxis heralded the development of SIT. Drawing from the experience of Kitasato and von Behring, William Dunbar in 1902 described his attempts at passive SIT using a horse- and rabbit-derived antipollen antitoxin for hay fever in humans. This technique was performed by instilling a powder or an ointment preparation of the antitoxin into the eyes, nose, and mouth for rhinitis symptoms and via inhalation for asthma.[3,15] In the same year, Charles Richet and Paul Portier provided the first experimental description of anaphylaxis while immunizing dogs with sea anemone toxin, a discovery for which Richet was awarded the Nobel Prize in Medicine.[3,16] Alexandere Besredka of the Pasteur Institute in 1907 furthered the knowledge of anaphylaxis by demonstrating that progressively increasing the doses of antigen resulted in protection from an anaphylactic challenge in a guinea pig model.[1]

With the foundational work now complete in establishing pollen as the cause of hay fever, success in passive protection via antisera, and the evolving understanding of the immune response to vaccination, the stage was set for Noon and Freeman's seminal investigation into active SIT. In 1911, both Noon and Freeman were working in Sir Almroth Wright's laboratory at St Mary's Hospital, London. Noon subscribed to the conceptual bases of Dunbar's earlier work, namely, that a toxin component of the pollen was responsible for generating the symptom constellation of hay fever and that

a pollen antitoxin would be protective from these effects. However, unlike Dunbar's attempts to passively transfer the antitoxin, Noon and Freeman developed a protocol of subcutaneous injections of pollen extracts with increasing doses according to a defined schedule for patients with hay fever. By so doing, they pioneered the first successful SIT trial. Beyond that, they recognized several fundamental tenets of SIT that continue to hold true in current clinical practice: the optimal dose interval is initially 1 to 2 weeks and that allergen overdose may induce anaphylaxis.[1] Although Noon died of tuberculosis prematurely in 1913 at 36 years, Freeman completed a trial of 84 patients with their SIT regimen, which was reported in the *Lancet* in 1914. Although not rigorously controlled, the trial nevertheless showed that allergen-SIT was effective in allergic patients and that it seemed to confer an acquired immunity lasting for at least 1 year after cessation of treatment.[4] After the success of Noon and Freeman, acceptance and incorporation of SIT expanded rapidly in clinical practice. Dr Chandler Walker established one of the first dedicated clinics for allergic patients at the Peter Bent Brigham Hospital in Boston, which was followed shortly by Dr Robert Cooke's clinic at New York Hospital in 1918.[1] Dr Cooke made numerous contributions to the nascent field of SIT, including the development of intradermal skin testing (extending Oscar Schoss's original scratch test, first established in 1912), the discovery with Mary Loveless of blocking antibodies in response to allergen-SIT, the introduction of the protein nitrogen unit for extract standardization, and the identification of house dust as a ubiquitous allergen.[3,5] Furthermore, he was a dedicated teacher and leader who provided crucial leadership as allergy/immunology began to be recognized as a distinct medical subspecialty and was vital to establishing the first training programs in this emerging field.[3]

By the 1920s, allergen-SIT was established as a viable and effective treatment of allergic conditions, including allergic rhinitis and asthma. Dr Arthur Coca was an influential force in the field during this decade, developing a reagent to extract allergens for use in skin testing. He founded the *Journal of Immunology* and is credited with coining the term atopy (derived from the Greek term "strangeness") into the allergic lexicon.[3,17] In addition, Otto Prausnitz and Heinz Küstner deserve mention during this time for their demonstration of passive transfer of hypersensitivity (in this case, fish hypersensitivity via intradermal injection of Küstner's serum into Prausnitz and challenge 24 hours later with intradermal injection of fish antigen). The eponymous P-K reaction refers to the reaction that occurs on allergen challenge after passive transfer of what is now known to be allergen-specific IgE (termed "atopic reagin" at the time by Coca) into a nonallergic subject.[3]

As SIT practice evolved, the technique was adapted for treatment of conditions beyond hay fever. In 1956, Dr Mary Loveless, mentioned earlier in connection with Cooke in the discovery of blocking antibodies, performed uncontrolled studies using SIT for Hymenoptera hypersensitivity. She found that whole-body insect extracts versus the use of pure isolated venom were ineffective to treat this disease.[3,18] She also devoted substantial effort to emulsified depot preparations of allergen for SIT, but it was later discovered that the emulsion preparation induced plasma cell dyscrasias in animal models and its use was not pursued further.[1] Bernard Levine and Charles Parker, working independently in the 1960s, defined the antigenic determinants responsible for penicillin hypersensitivity, which ultimately led to successful desensitization protocols for allergic patients requiring this crucial antibiotic.[3,19,20]

Perhaps equal in significance to the Noon and Freeman's first clinical trial of SIT is the discovery of the fundamental molecule of allergy, IgE. Two research teams working via dissimilar experimental avenues arrived at the same conclusion that a new class of immunoglobulin molecules must be the cause implicated in hypersensitivity. The husband and wife team of Kimishige and Teruko Ishizaka isolated a novel

immunoglobulin fraction from a patient with extreme ragweed hypersensitivity and demonstrated its ability to fixed radiolabeled allergen.[7,21] They designated this molecule gamma E globulin, for its ability to create erythema in the skin in a P-K reaction. Separately, Hans Bennich and SGO Johansson isolated a unique immunoglobulin from a patient with myeloma, terming it IgND, so named for the patient's initials.[8] Translating this finding to atopic individuals, IgND was elevated in patients suffering from allergic rhinitis or allergic asthma. In 1968, the World Health Organization (WHO) convened an international conference in Lausanne for comparative analysis of the collective data from these two research groups and determined that both groups had discovered the same molecule. The conference concluded with the designation of a new immunoglobulin class, IgE.[21] This milestone represents a watershed moment in the immunology of allergic diseases, because IgE is the fundamental triggering factor for mediators released by mast cells and basophils. Its impact resonates still with the development of omalizumab, a targeted anti-IgE monoclonal antibody that has proved invaluable in severe allergic asthma.

By the late 1960s, allergen-SIT was in common practice, although its efficacy had not yet been rigorously demonstrated in controlled trials. The first double-blind controlled trial was reported in 1965 by Lowell and Franklin,[6] establishing efficacy of SIT using ragweed extract in adult patients with allergic rhinitis. Fontana and colleagues[22] followed in 1966 with the first controlled study of SIT in the pediatric population, which did not show a difference between the treatment and control groups (although this study looked only at the presence or absence of symptoms, as opposed to the degree of severity). However, in 1969, Sadan and colleagues[23] published a controlled trial in children, unequivocally demonstrating a marked decrease in the symptom severity scores and an increase in blocking antibody levels in pediatric patients given SIT to ragweed extract for seasonal allergic rhinitis. Norman and colleagues[24] extended these observations, showing that SIT with antigen E (now known as Amb a 1, the major ragweed antigen) was equal in efficacy to that with whole ragweed extracts in ragweed-sensitive patients and was better tolerated, generating fewer systemic and local reactions.

By the 1970s, SIT for stinging insects was investigated by many groups. A landmark study was published in 1979 by the Hopkins group, led by Larry Lichtenstein, showing the clinical superiority of venom SIT versus whole-body extracts in insect hypersensitivity.[9] In 1974, Dr Richard Lockey was among the first to recognize in an international medical journal that hypersensitivity to imported fire ants and other stinging ants can cause a systemic reaction identical to that seen with other Hymenoptera.[25] Dr Lockey and his colleagues extended their findings to the identification of fire ant venom allergens prepared from whole-body extracts using sera from sensitized patients via immunoblotting.[26] Finally, the largest longitudinal study to date of venom SIT using US Federal Drug Administration standardized extracts was completed from 1979 to 1990, with the enrollment of more than 1400 patients into a venom immunotherapy (VIT) program. The results of this broad study demonstrated the overall safety of VIT, with a net incidence of 12% treatment-related systemic reactions, none of which were fatal.[27]

Although the 1970s and 1980s saw considerable work in demonstrating the efficacy and safety of SIT, the development of standardized extracts over the last 20 years has greatly enhanced the ability of allergists to deliver SIT of an accurate and consistent bioactivity. In the United States, there are now 19 standardized extracts, whose production is governed by current good manufacturing practice and whose potency is assured via standardized assays. The responsibility for the oversight of these procedures rests with the Center for Biologics Evaluation and Testing, a division of the US

Food and Drug Administration. In essence, there are two vital components to the standardization of a given allergen in the United States: an initial reference assessment of allergenicity known as the ID_{50} EAL method, which uses highly allergic individuals to a given allergen to comprise a reference standard, and a lot release limit assay, which is an in vitro assay (often a competition enzyme-linked immunosorbent assay) designed to ensure bioequivalence between different lots of standardized allergen. The situation in Europe is markedly different, where the onus is on the manufacturer to provide assurance of lot-to-lot consistency, without the use of an external reference standard.[28] There is, however, an ongoing effort in the European Union (the CREATE project) to develop international reference allergen standards.[29]

In 1998, WHO released a position paper that validated the accumulating body of work into the safety, efficacy, and standardization of allergen-SIT. Despite SIT being in practice for more than 80 years, this approbation nevertheless represented a landmark moment in the field, as members of all the major allergy and immunology organizations convened in Geneva to discuss the current state of the knowledge in the field and formulate the position paper. The committee concluded that allergen immunotherapy is safe (but noted the risk of anaphylaxis) and is indicated for allergic rhinitis/conjunctivitis, Hymenoptera hypersensitivity, and allergic asthma. They stressed the importance of appropriate patient selection, in particular those who had failed pharmacotherapy because of either intolerance or inadequate symptom control, and cautioned that SIT should only be prescribed by a knowledgeable allergist and administered in a clinical setting equipped to deal with the rare (but real) risk of systemic reaction.[30]

One lingering question that remained by the late 1990s revolved around the persistence of the clinical efficacy of SIT after treatment cessation, that is, whether a lasting modification of the immunologic response to a given antigen could be induced. The general recommendation had been for a treatment period of 3 to 5 years (including those of the WHO position paper, mentioned earlier), but data for the continued suppression of symptoms were lacking until Durham and colleagues[11] published a double-blind controlled trial in the *New England Journal of Medicine* in 1999 to address this question. Their work demonstrated a persistent reduction in symptom score and T-cell skin infiltration for up to 3 years after discontinuation of SIT; these changes were indistinguishable from the control group who remained on SIT during the same time frame. More recently, Jacobsen and colleagues[31] have demonstrated that a 3-year course of immunotherapy shows persistent improvement in rhinoconjunctivitis up to 7 years after the cessation of therapy and may also prevent the development of asthma in the pediatric population.

Thus far, this history has focused on subcutaneous immunotherapy (SCIT), but it should be noted that sublingual immunotherapy (SLIT) has become a recognized and accepted part of allergy practice in many parts of the world. Although limited in scope, Scadding and Brostoff[32] reported the first double-blind controlled trial with SLIT in 1986, wherein they reported improvement in symptoms and nasal flow rate after treating a small cohort of dust mite allergic patients. Passalacqua and colleagues[10] confirmed and extended these findings, noting not only decreased symptom scores in patients treated with dust mite SLIT but also diminished conjunctival inflammatory cell infiltrate and intercellular adhesion molecule 1 expression. Since 1986, there have been more than 60 controlled clinical trials with SLIT, most of which have used monomeric therapy to either dust mite or grass pollen. A 2009 World Allergy Organization position paper confirmed the efficacy and safety of SLIT for grass allergens in both adults and children.[33] Finally, the Durham group demonstrated lasting clinical efficacy of SLIT, observing sustained symptom control in grass-allergic subjects for 1 year after cessation of a 3-year treatment period.[12]

Although allergen-SIT, as is currently administered, has proved enormously beneficial to a broad spectrum of allergic patients, there is clearly a lack of uniformity in response to therapy and there remains the small but real risk of systemic reactions (including life-threatening anaphylaxis) during subcutaneous injection. This risk was documented in the almost simultaneous reports by Lockey and colleagues[34] and the British Committee on Safety of Medicines[35] about a number of deaths associated with SCIT. Given the objective of the safest and most effective therapy, there are multiple new investigational approaches that are being explored to deliver SIT. One approach to improving safety has been to add anti-IgE treatment (omalizumab) during initiation of SCIT. Initial trials of this approach indicate improved safety, with significantly few systemic reactions in the omalizumab group.[36] Another strategy is immune modification via targeting of toll-like receptors (TLRs). A TLR4 agonist (Pollinex) has been licensed in the United Kingdom and shown to reduce symptom scores, skin reactivity, and allergen-specific IgE levels in both adults and children with sensitivities to grasses, trees, or ragweed. However, initial trials in the United States have been suspended because of an ongoing investigation of an adverse event with this product.[36] TLR9 is also a potential therapeutic target via administration of cytidine-phosphate-guanosine (CpG) immunostimulatory sequences either in conjugation with allergen or alone. Initial trials with CpG-conjugated Amb a 1 were promising, but there were problems with the study design that led to inconclusive data.[37,38] Trials using CpG sequences packaged as virus-like particles are ongoing.[36] Both recombinant and peptide allergens have been actively investigated, with the goal to increase the safety of administration while preserving the immunomodulatory properties of the allergen preparation. Alternative administration routes beyond SCIT and SLIT represent another possibility for allergen delivery. The most novel among these is intralymphatic injection of allergens, which in a study of 165 grass-allergic subjects showed comparable symptom reduction with 3 intranodal doses (given over two months) versus standard SIT administered over three years.[39]

Although it is impossible to mention every individual who contributed to the development of allergen-SIT, many of the highlights in the progress toward and since the advent of SIT have been reviewed and moreover, we hope, have engendered a sense of respect and admiration for the physicians and scientists who labored diligently to provide a novel and effective technique to alleviate the suffering of those with allergic conditions. Many mysteries still abound in the understanding and treatment of immunologic disease. While we acknowledge the contributions of those whose experiments lead to an efficacious and enduring therapy for over one hundred years, new innovative modalities will incorporate genomic and molecular advances as progress continues toward the ultimate goal of safe, specific, and even curative treatments for allergic disease.

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