

# The Evolution of Understanding Inhalant Allergy

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## KEYWORDS

Inhalant allergy • Atopy • Immunotherapy • Skin testing  
Pharmacotherapy • Allergen • Immunoglobulin E

## Key Points: UNDERSTANDING INHALANT ALLERGY

- From the later half of the 1800s to the early 1900s, allergy, infectious disease, and immunology practitioners were one and the same, with the view that sensitivity to pollen toxin could be addressed in the same way vaccination or subcutaneous injection remedied susceptibility to bacterial diseases. It was not until 1955 that bacterial vaccines became uncommon in the treatment of intrinsic asthma or chronic rhinitis.
- In the first half of the twentieth century, the basis for much of what we currently practice, from skin testing to progressive dose escalation immunotherapy, was derived empirically from uncontrolled (single arm, unblinded) clinical studies with nonstandardized extracts. The efficacy of combining multiple allergens in a treatment regimen went largely unverified.
- In the 1920s, observations that house dust and climate allergens could cause rhinitis and exacerbate asthma failed to gain the attention of allergy practitioners. It was not until 1960s when dust mite was characterized that environmental modification joined the prior triad of treatment (counseling, pharmacotherapy, and immunotherapy).
- Oral immunotherapy was common in the United States until a multi-institutional trial in 1940, with the negative result now ascribed to the ineffective pill route of administration. Positive reports from European centers over the intervening period have caused a recent resurgence in interest.
- Beginning in the mid-1950s, clinical trials began to incorporate placebo controls and subject/doctor blinding, moving the practice of allergists from empiric- to evidence-based practices. Oral immunotherapy still trails injection therapy in corroborating data. Recently, organized allergy has promulgated practice parameters from patient testing to allergen standardization and administration and has agreed on standards for future studies.

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## EARLIEST HISTORY

The first inklings that one's native reaction to a toxic substance could be altered may have originated with Mithridates (131–63 BC), a king of Pontus in Asia Minor.<sup>1,2</sup> Because poison was a common way to dispatch rivals in those days, the king began ingesting small amounts of the potential poisons in gradually increasing doses until he developed resistance. Vague references to alterable capabilities of the immune system thereafter surfaced sporadically,<sup>2</sup> from Galen and others, but it was not until 1891 that Ehrlich<sup>3</sup> confirmed the ability to induce tolerance in mice fed ricin, a potent toxin, after a prolonged and gradual dose escalation. The distinction between resistance to toxin, or to infection, now known to be principally IgG and/or IgA mediated, and hypersensitivity diseases, principally IgE mediated or cell mediated, was indistinguishable to physicians until 1915 when verbiage related to a toxin (poison to infection) as the inciting factor for allergic rhinitis or asthma was abandoned in favor of the concept that such was a localized manifestation of anaphylaxis.<sup>4</sup> In 1923, an allergy interest group was formed, and subsequently the *Journal of Allergy*, within the members of the American Association of Immunologists, which itself did not have sufficient numbers to be self-sustaining until 1913.<sup>2,5</sup> Skepticism in the scientific community about both disciplines was characterized by an admonition to the society's first journal editor that "immunology is dead."<sup>5</sup>

## EIGHTEENTH AND NINETEENTH CENTURY CONTRIBUTIONS

Many investigators in the eighteenth and early nineteenth centuries who empirically derived much of the basics of what is still practiced clinically, from skin testing to progressive allergen dose escalation, were themselves afflicted with allergic rhinitis, chronic rhinosinusitis, and/or asthma. Pharmacologic alternatives were sparse, and there was no agreement on the nature of inhalant sensitivities. An article by Bishop<sup>6</sup> in the first issue of *Laryngoscope* espoused a formula of morphine, atropine, and caffeine, laying the blame for seasonal rhinitis to an excess of uric acid in the blood. Adrenaline did not become commercially available until 1904, ephedrine until 1924, the first sedating antihistamine until 1936, and widespread release of steroid preparations until the mid-1950s.<sup>1,7</sup> Given this dearth of effective remedies, it is not surprising that many investigators devoted their professional careers sorting through the confusing, given few laboratory-based assays, morass of hypersensitivity disorders to identify effective treatments. The efforts of some prominent contributors in allergy and related immunology are detailed.

The concept of an epicutaneous or transcutaneous route for conferring resistance started in 1795 with Jenner,<sup>8</sup> who used a prick into a subject's skin to deliver material derived from a cowpox pustule, which over time afforded protection from the more virulent smallpox virus. Jenner named the process vaccination (Latin reference to cow). In 1879, Pasteur<sup>9</sup> demonstrated that a weak cholera strain given to chickens also provided protection from virulent strains and then replicated this procedure for anthrax in sheep. Pasteur chose a term just appearing in English literature, immunizes, for this phenomenon and, in 1884, successfully applied a series of graduated subcutaneous inoculations for rabies prevention. However, there were issues including significant reactions in some cases, now known to be from antineural autoantibodies. In the same time frame, Koch<sup>10</sup> reported delayed hypersensitivity responses in some samples in which he had given tuberculosis culture inoculations with the hope of conferring immunity. These untoward effects encouraged alternate approaches, and by 1891, von Behring and Kitasato<sup>11</sup> had successfully conferred passive immune protection to diphtheria in human patients injected with serum containing antitoxin from previously infected animals (usually horse).

However, reports of adverse reactions surfaced yet again, with the first fatality in 1896, soon joined by others, suppressing enthusiasm for passive immunization to other infectious diseases prevalent in that era. In an effort to identify what might be causing these issues and also to introduce some standardization to antisera preparations, Ehrlich<sup>12</sup> identified in the laboratory what is now known to be an antigen-antibody reaction as the culprit behind anaphylactic reactions to nonhuman sera.

The first description of the classic symptoms of hay fever and asthma were penned by Bostock<sup>13</sup> in 1819, describing his personal illness. It was not until 1872 that Wyman<sup>14</sup> tentatively identified pollen as a cause of autumn catarrh in the United States. The next year in England, Blackley<sup>15</sup> followed with the same observation and a critical concept, not fully accepted for hay fever until 1915 and asthma until the 1940s, that inhalant sensitivities were not the result of an infectious disease. Blackley was the first to try immunotherapy, a self-experimentation whereby he rubbed grass pollen into his abraded skin, following up in 1880 with observations on the cutaneous wheal, erythema, and pruritus response to what was essentially a scratch test and using such to detect and grossly quantitate patient sensitivity.<sup>16</sup>

## EARLY TWENTIETH CENTURY CONTRIBUTIONS

The concepts of passive versus active immunity, anaphylaxis, and hypersensitivity were sorted out during the first 15 years of the twentieth century. von Pirquet<sup>17</sup> was able to distinguish a basic difference between systemic horse serum reactions and a local response to smallpox vaccination, stating that, “immunity and hypersensitivity can plus be closely related” and introducing the term allergy from *allos* (other or altered state) and *ergon* (work) for the former phenomenon.<sup>18</sup> von Pirquet proposed the term allergen for a substance that stimulates an organism to change its intrinsic response after prior exposure to that substance. Attempting to answer the question of why an immunized organism could be protected from or supersensitive to the same disease or substance, Pirquet tracked the progressively shortening interval to reactions to successive horse serum antitoxin injections in affected individuals, postulating a collision of antigen and antibody as per Ehrlich’s concept. The investigator added the distinction that because of previous exposure, the body was changed by antibodies and hence the heightened response. How to minimize these adverse reactions consumed the efforts of many. In 1907, Besredka and Steinhardt<sup>19</sup> demonstrated in an animal model that injections of progressively larger but tolerable doses of antigen, like that of Ehrlich’s mice fed ricin, eventually conferred protection from an adverse response. This observation reinvigorated clinical interest in injection therapy for hay fever and asthma, although there were still continuing issues (which continue today), with acute asthma attacks being incited in some.

Curtis<sup>20</sup> in the United States was an early proponent for injection therapy, albeit with very dilute pollen extracts. Although the details were sparse, Curtis reported some success with injection therapy as well as oral administration in the same dosages. In Germany, Dunbar<sup>21</sup> was still pursuing the antitoxin route then being practiced for diphtheria and tetanus, applying a horse and rabbit serum antipollen preparation variously into the conjunctiva, nose, or mouth or via aerosolized oral inhalation, inciting occasional life-threatening reactions, which convinced most investigators that passive immunization for hypersensitivity diseases was a dead end. However, the investigator did develop a method of testing, whereby pollen extracts were applied to a subject’s conjunctiva to identify specific sensitivities. This diagnostic approach became widespread and was adopted by Noon<sup>22</sup> who was practicing at St Mary’s Hospital in London, a major center for chest diseases.

Noon added a measure of quantification to the conjunctivally applied extracts, which he thought contained a plant toxin, setting that amount extracted from a thousandth part of a milligram (ie, a microgram) of a pollen sample as 1 “Noon unit.” Noon subdivided patients into those who were very sensitive, reacting to 4 or fewer Noon units; those with intermediate sensitivity, reacting to a 70-unit threshold; and those who were nonallergic, reacting to no less than 20,000 units.<sup>22,23</sup> The investigator chose subcutaneous injections, still called inoculations, of the same extract as for testing preseasonally and/or coseasonally at 5- to 10-day intervals for 2 months (**Fig. 1**). Although Noon’s approach varied considerably among patients, he seemed to use higher doses of the extract in lesser-sensitive patients. Noon eventually settled on an optimum interval between injections of 1 to 2 weeks and noted that local or systemic reactions increase if the injections were too frequent or excessive in extract dose. He documented diminished conjunctival reaction to allergen challenge after pre-seasonal therapy. Noon’s personal issue with tuberculosis necessitated his withdrawal from practice (died 2 years later), and he transferred ongoing investigations to his partner and a hay fever sufferer, Freeman.<sup>24</sup> Freeman established that some symptom relief persisted for at least a year after discontinuing the injections and noted that some individuals were also less troubled by asthma.<sup>23,24</sup> The investigator introduced the concept of a placebo effect with immunotherapy, observing a “constant tendency to detect such improvements in adventitious fluctuations in health” and noting the potential for physician or patient bias or external circumstances such as a heavy or light pollen season. Freeman<sup>25</sup> marketed Noon’s toxin solution via the Parke Davis pharmaceutical firm. By 1920, Freeman reported experience with more than 200 pollen-sensitive patients (no controls), had discarded the 2-per-day limitation of conjunctival testing in favor of batteries of scratch tests, and was experimenting with injections for food and animal sensitivities (**Fig. 2**). The investigator also suggested the option of rush immunotherapy over a day or two, an approach now used for vespid or in-hospital drug hyposensitization.<sup>26</sup>

## EARLY ORGANIZATION OF ALLERGY TESTING AND TREATMENT

From 1914 to the 1950s, most published clinical allergy experience shifted from Europe to the United States, with Koessler<sup>27</sup> in Illinois and Goodale<sup>28</sup> in Massachusetts, the former investigator reporting positive results with 45 patients. Goodale had established

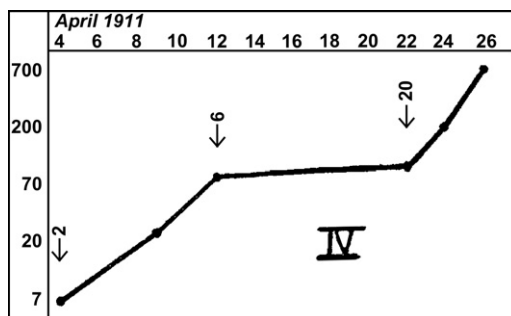


**Fig. 1.** The x-axis denotes the number of conjunctivally applied drops of timothy pollen extract in Noon units that were required to incite a response and the y-axis, when subcutaneous injections of such extracts were given during immunotherapy. The numbers adjacent to the arrows indicate the strength in Noon units of each injection. (From Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;177:153, figure. 1; with permission.)

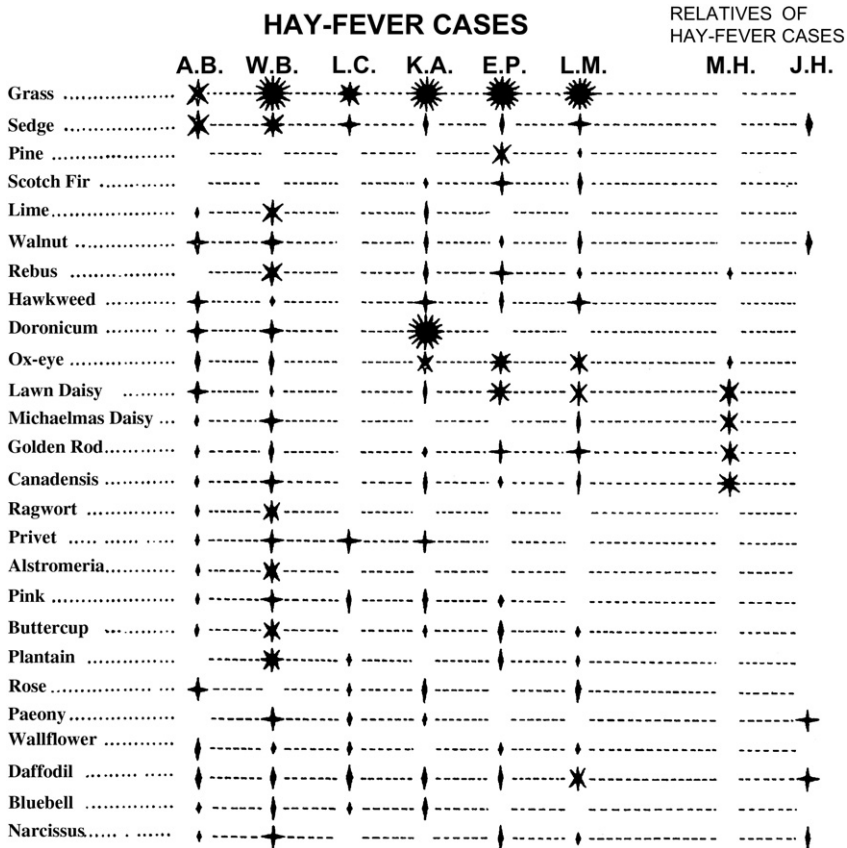


**Fig. 2.** Six-level classification of scratch test reactions to pollen extracts in 6 patients and 2 relatives of such. To some degree (details not fully clear), the starting dose for subcutaneous immunotherapy was determined by patient sensitivities (ie, lower starting dose if higher sensitivity). (From Freeman J. Toxic idiopathies: the relationship between hay and other pollen fevers, animal asthmas, food idiosyncrasies, bronchial and spasmodic asthmas. Proc R Soc Med 1920;13:137, diagram 7; with permission.)

the first university-based allergy clinic in the United States in the Department of Laryngology of the Massachusetts General Hospital, where he enjoyed a career-long collaboration with medicine colleagues Rackemann and Colmes<sup>29</sup> whose interest was asthma. A year later, Cooke established an allergy practice in the Department of Medicine at Cornell, where he also benefited from the presence of a learned colleague, Coca, who was running a fledgling immunology lab and later became the first editor of the *Journal of Immunology*.<sup>5,29</sup> Cooke, who in the 1920s was a founder of both the first US allergy society and the *Journal of Allergy*, was striving to understand a personal affliction.<sup>30</sup> He had had severe asthma during childhood, which vanished during sojourn in boarding school, and it became apparent that his major sensitivity was toward horses. During an obligatory 6-month internship rotation on a horse-drawn ambulance in New York City, Cooke observed that this would not have been possible save for his adrenaline kit, stating “I put as much adrenaline under my skin as any human being.”<sup>30</sup> After assisting a tracheotomy in a patient with diphtheria, and hence obliged to a prophylactic injection of horse serum antitoxin, the investigator

lapsed into unconsciousness for 10 hours, requiring intubation. In his 1915 publication,<sup>4</sup> choosing Goodale's preferred journal, *Laryngoscope*, Cooke eschewed pollen toxin as the source of hay fever in favor of the pollen inciting a sensitization that could manifest as either localized (rhinitis, asthma) or systemic anaphylaxis. The investigator postulated that immunity to infection likely resulted from induction of a widely circulating antibody, which for anaphylaxis was from a mostly tissue-fixed antibody. Observing that most sufferers had multiple sensitivities, Cooke preferred wide batteries of intracutaneous skin tests in a clinic session along with the scratch tests Freeman favored and prick tests that had been introduced in 1908 by Mantoux as he searched for the best method to apply a tuberculosis skin test. All 3 cutaneous testing methods remained in common use until 1987, when issues with reproducibility of scratch tests led the American Medical Association to recommend against routine use.<sup>31–33</sup> Cooke tested for a wide variety of pollens as well as foods, including lobster, although only treated for inhalants.<sup>30</sup> Extracts of varying strengths were used to classify patients into 4 levels of sensitivity, and to some degree, the initial injection dose was determined by such, ranging from 5 to 100 Noon units. Most treatment was preseasonal, although coseasonal was an option. The usual regimen was to start with a low dose and escalate weekly, beginning as Noon about 2 months before the relevant season. After a report on the aforementioned in 140 patients, Cooke teamed with VanderVeer (1916) to detail the medical histories, with emphasis on a possible inherited predilection to allergic diseases, of 621 patients.<sup>34</sup> The investigators noted a familial tendency for asthma, allergic rhinitis, angioneurotic edema, and immediate food sensitivities but had insufficient evidence to include eczema. However, by the 1920s, Coca was using atopy to describe the trio of hay fever, asthma, and eczema. The incidence of inhalant allergy in the New York area was estimated by Cooke at 10%, of whom 42% had multiple sensitivities.<sup>34</sup> Cooke noted that, "sensitized individuals transmit to their offspring not their own specific sensitization but an unusual capacity for developing bioplastic reactivities to any foreign protein." Although the conclusion was that hypersensitivity was transmitted as a dominant characteristic, it did not fit the simple mendelian pattern; so the question remained open.

Immunotherapy for asthma or rhinitis was confined to pollen sensitivities until 1921 when Kern<sup>34</sup> identified house dust as the causative agent in many cases. However, the major allergen, mite, was not isolated until 1959,<sup>35</sup> and extract preparations until then were as varied among practitioners and commercial sources as any in immunotherapy; not unexpectedly, reports on effectiveness varied. Cooke and others began adding dust and many other nonstandardized allergens into testing and treatment mixes, but there were few published reports, none major, establishing efficacy. It was not until 1954 that the first placebo-controlled trial of immunotherapy for basic pollen sensitivity was published.<sup>36</sup>

van Leeuwen and colleagues in 1924 observed the presence of climate allergens that could exacerbate asthma and rhinitis.<sup>37</sup> The first allergen-free hospital rooms were fitted, and the substantial relief produced in asthma patients brought to the attention of the medical community the potential effect of environmental modification beyond the simple advice to avoid outdoor activities during problematic pollen seasons. Without specifically identifying molds as the issue, the investigators established that damp sleeping quarters were bad for asthma patients, whereas dry mountain areas were favorable.<sup>37–39</sup> Curiously, recommendations for environmental measures for patient homes or places of employment did not gain traction in the allergy community until the 1980s when within a decade there was an explosion of publications distributed across the world's literature and the introduction of the hygiene hypothesis.<sup>40,41</sup>

## EARLY USE OF BACTERIAL VACCINES FOR ALLERGY

Another common practice during the early years of immunotherapy was the use of bacterial vaccines for asthma and/or chronic rhinitis. This practice was first mentioned by Allen<sup>42</sup> who in 1908 applied an autologous nasopharyngeal vaccine for chronic rhinitis (infectious or allergic, it seems). Lowdermilk<sup>43</sup> advocated combining pollen and bacterial extracts in the same injection for the patient with both seasonal rhinitis and sinusitis issues. Bacterial vaccines were adopted for patients with sinusitis by Goodale and for selected asthma patients by his colleague, Rackemann,<sup>29</sup> who thought intrinsic asthma was possibly of bacterial origin, unlike the better-characterized extrinsic variety that was correctly ascribed to inhalant hypersensitivity.<sup>1</sup> Cooke<sup>44</sup> later became a proponent, correctly making the distinction that injections for allergies and those for bacterial issues caused different bodily responses, one being hyposensitization and the other immunity. This insight was confirmed by his colleague, Coca, who established in 1925 that a heat-labile reagin (now known to be IgE) was responsible for positive skin test results and hypersensitivity reactions and that a heat-stable antibody called blocking antibody (now known to be IgG) was induced by immunotherapy.<sup>30,44–47</sup> Enthusiasm for bacterial vaccines did not wane until the advent of antibiotic therapies in the 1940s allowed trials of such in asthma patients to no effect. As a final blow, in 1955, the first controlled study of bacterial vaccines was reported by Franklin, followed within a few years by other negative studies, removing mixed respiratory or autologous bacterial vaccines from the practices of most allergy practitioners (Fig. 3).<sup>48</sup>

## POLLENS AND EARLY STANDARDIZATION ATTEMPTS

The distribution of various pollen types, and their seasonal variations in the United States (eg, earlier and shorter spring, summer, and fall seasons in northern

| Results of Treatment |            |           |                      |                    |                     |                     |
|----------------------|------------|-----------|----------------------|--------------------|---------------------|---------------------|
| Score                |            | H         |                      | F                  |                     |                     |
|                      |            | Vaccine   | Control              | Vaccine            | Control             |                     |
| -11<br>-7-10<br>-3-6 | } Worse    | ..        | { 0<br>1<br>5 } 6    | { 2<br>1<br>2 } 5  | { 5<br>3<br>4 } 12  | { 1<br>1<br>8 } 10  |
| -2<br>+2             |            | No change | ..                   | 13                 | 13                  | 11                  |
| +3+6<br>+7+10<br>+11 | } Improved | ..        | { 10<br>16<br>5 } 31 | { 8<br>9<br>4 } 21 | { 9<br>15<br>3 } 27 | { 1<br>14<br>8 } 23 |
|                      |            |           | 50                   | 39                 | 50                  | 45                  |

**Fig. 3.** Experience of 2 investigators (H and F) with bacterial vaccine or saline placebo administered every 1 to 2 weeks for 1 year in 184 patients, divided into vaccine and placebo injection groups, with intrinsic asthma; vaccines were prepared per nasal swab results for each patient and variously included *Haemophilus influenzae*, *Streptococcus viridans*, *Moraxella catarrhalis*, and *Bacillus subtilis*. There were no symptom differences between the active and placebo arms at 1 year. (From Frankland A, Hughes W, Garrill R. Autogenous bacterial vaccines in the treatment of bronchial asthma. Br Med J 1955;2:943, table VII; with permission.)

locales), was ascertained by a nationwide survey of allergists by Durham in 1929.<sup>49</sup> Two years later, Thommen<sup>50</sup> cited 15 studies by different investigators, all but 1 of which detailed a positive experience with pollen extract therapy and also a few that included house dust. The investigator postulated guidelines for assessing the burgeoning number of potential allergens being added to immunotherapy regimens, with little to establish efficacy, by various allergy practitioners with internal medicine, pediatric, or otolaryngologic backgrounds, stating these allergens must be airborne and in sufficient quantities to incite a hypersensitivity response. It remains challenging (in fact impossible) to compare reports from the plethora of investigators in this era because most studies were small series with little standardization of skin testing or extract preparation beyond the basics described in 1911 by Noon. This lack of standardization was recognized by Coca<sup>45</sup> who developed an assay for the total nitrogen content in an extract, acknowledging that this and allergenic activity were not always identical. Then in 1933, Cooke and colleagues,<sup>51</sup> took another step toward allergen quantization with an assay of protein nitrogen units (PNUs), an alternative to the traditional weight per volume (W/V). Just as importantly, the investigators observed that the extract mixtures did not possess permanent potency but deteriorated depending on the passage of time, diluents selected, and other allergens in the mix. These laboratory-based advances encouraged the 2 precursor organizations of the American Academy of Allergy to meet in 1935 with the goal of standardizing practices.<sup>52</sup> The organizations were unable to reach a consensus but did concur that skin test results do not always correlate with patient manifestations and hence the clinical judgment of a trained practitioner was critical. There was no agreement on extract preparation/storage and also on an optimal testing method, with scratch, prick, and intradermal approaches common, and some preferred oral administration to injection administration of allergen. Black<sup>53</sup> had reported lower nasal responses to ragweed extract after oral immunotherapy, although 12 years later followed up with a wider yet less-favorable experience when comparing oral therapy with injection therapy.<sup>54,55</sup> Stier and Hollister (1937) reported a 3-year experience, achieving an improvement of 78% with oral drops of pollen allergen extracts in concentrations up to 1:100 W/V.<sup>56</sup> Bernstein and Feinberg<sup>56</sup> compared the amount of allergen that is required to produce equivalent relief if given orally versus subcutaneously and established that the oral route required the larger amount. Confusion was such that in 1940, Feinberg and colleagues<sup>57</sup> assembled a multiuniversity trial on 103 subjects who took oral immunotherapy or placebo and another 57 who took injections or placebo and found that although only 25% experienced relief with oral therapy, 56% did with shots (**Fig. 4**).<sup>58</sup> This diminished enthusiasm for oral therapy in the United States, although some investigators, such as Hansel, were still experimenting with sublingual drop administration in the 1970s.<sup>57</sup> This approach has since been demonstrated to be valid by the European allergy community, and hence, interest in this alternative among US practitioners has returned in the past decade.<sup>59</sup> It is notable that Feinberg and colleagues<sup>57</sup> chose to administer the oral extract in pill form, which is likely the reason that 12.5% of patients experienced major gastrointestinal symptoms, whereas current thinking specifies an interval of oral retention to allow uptake by Langerhans cells in the oral submucosa. The gastrointestinal reactions also limited enthusiasm for oral immunotherapy for contact dermatitis. Shelmire<sup>60</sup> had advocated a similar method for poison ivy after patch test verification of sensitivity, following a common remedy in the homeopathic, native American, and folk medicine communities in earlier decades.<sup>1</sup>

*Summary of Study of Oral Pollen Therapy.*  
*Rush Medical College, University of Chicago*

| Type of Cases                         | Oral Group*         | Parenteral Group † |
|---------------------------------------|---------------------|--------------------|
| A. Total number of cases.....         | 32                  | 25                 |
| B. In 1938, hay fever only.....       | 18                  | 10                 |
| C. In 1938, hay fever and asthma....  | 14                  | 15                 |
|                                       | (44% of A)          | (60% of A)         |
| <hr/>                                 |                     |                    |
| Treatment in 1939 Season              |                     |                    |
| D. Average number of doses.....       | 40                  | 14.4               |
| Variation.....                        | (23–62)             | (7–21)             |
| E. Average maximum daily dose.....    | 116,000             | 2,452              |
| Variation.....                        | (60,000–120,000)    | (700–4,500)        |
| F. Average total course dose.....     | 3,237,000           | 16,817             |
| Variation.....                        | (675,000–5,113,000) | (1,930–41,320)     |
| <hr/>                                 |                     |                    |
| Results of Treatment                  |                     |                    |
| G. In 1939, hay fever only.....       | 10                  | 10                 |
| H. In 1939, hay fever and asthma....  | 22                  | 15                 |
|                                       | (69% of A)          | (60% of A)         |
| I. In 1939, asthma for first time.... | 9                   | 2                  |
|                                       | (50% of B)          | (20% of B)         |
| <hr/>                                 |                     |                    |
| Comparison with 1938 Season           |                     |                    |
| J. Symptoms same .....                | 3 (10%)             | 7 (28%)            |
| K. Symptoms better .....              | 8 (25%)             | 14 (56%)           |
| L. Symptoms worse .....               | 21 (65%)            | 4 (16%)            |

\* Received oral pollen and saline injections.

† Received pollen extract injections and placebo capsules.

**Fig. 4.** Oral pollen immunotherapy, in pill form, was compared with subcutaneous immunotherapy for grass pollen delivered coseasonally. Allergen doses (nonstandardized extracts) were much higher in the oral than in the subcutaneous preparations, and gastrointestinal side effects in the former group were severe in 12.5% and minor in another 12.5%. No anaphylactic reactions were encountered. (From Feinberg S, Foran F, Lichtenstein M. Oral pollen therapy for ragweed pollinosis. *J Am Med Assoc* 1940;115:27, table 2; with permission.)

Hansel, called the “father of otolaryngic allergy” after the publication of his textbook on allergy and rhinology in 1936, had also served as a president of the American College of Allergy.<sup>61,62</sup> The investigator advocated intradermal testing for quantification of sensitivity, selecting a 1:10 serial dilution technique, which became a common tool in basic clinical investigations, including that by Voorhorst and colleagues<sup>63</sup> in 1964 when establishing dust mite as a major allergen and the current regimen for vespid sensitivity testing.<sup>32,62,64,65</sup> Rinkel,<sup>65</sup> a brief understudy of Hansel’s, in 1949 introduced a 1:5 variation that became the standard within the otolaryngologic community.<sup>66,67</sup> By whatever scheme, the serial dilution approach not only identified the degree of patient sensitivity to a particular allergen but also served as a rough guideline to the extract concentration at which immunotherapy could be safely initiated.<sup>32,66,68</sup> Serial dilution was also adopted by the US Food and Drug Administration (FDA), a 1:3 approach described by Turkeltaub and colleagues<sup>68</sup> in 1986 to quantify in subjects of known sensitivity the potencies of extracts submitted for commercial distribution.

## BEGINNING OF PLACEBO-CONTROLLED TRIALS IN IMMUNOTHERAPY

The 1950s ushered in the first large evidence-based studies of skin testing and immunotherapy protocols and the following decade, the first useful laboratory assays beyond the crude measures for reagin and blocking antibody and passive transferability with the Prausnitz-Kustner technique. The aforementioned said, it was remarkable what the allergy practitioners and immunologists previously detailed had accomplished with limited investigations with nonstandardized extracts in modest patient populations. The downside was that there remained a wide variety of practices, some now known to be suboptimal to ineffective, that warranted scrutiny via an evidence-based approach. Feinberg and colleagues<sup>57</sup> in their placebo-controlled study of oral immunotherapy in 1940, selected an ineffective route for administration. It was not until 1954 that Franklin and Augustin,<sup>36</sup> in the same London hospital in which Noon had practiced, reported a placebo-controlled trial of injection immunotherapy on 200 subjects. The investigators compared crude pollen extract (little changed from Noon's) with a purified pollen protein (PNU, as Cooke advocated) and phenolized saline. There was a response greater than 75% to the pollen extracts, and 33% for the saline group, establishing what was first described by Freeman<sup>25</sup> as the placebo response (25%–35%) intrinsic to allergen therapies. As mentioned previously, Frankland and colleagues<sup>48</sup> had reported a controlled, and negative, study of bacterial vaccines that same year. In 1965, Lowell and Franklin<sup>69</sup> published a double-blind placebo-controlled (DBPC) study using ragweed symptom and patient medication scores as outcomes measures, setting a new baseline for the minimum measures for randomization and outcomes measures expected for allergy-related studies. The investigators suggested that serial measurement of neutralizing or blocking antibody might in the future be suitable to quantitate response to immunotherapy independent of cumbersome clinical trials, a goal still not met. In 1968, Norman and colleagues<sup>70</sup> adopted the DBPC approach to a 4-year comparison of whole ragweed extract with the newly identified major allergen in ragweed, antigen E, the latter better tolerated both systemically and locally. To ensure that the placebo group is not detected by subjects or practitioners, the investigators added histamine to the placebo injections. Antigen E in micrograms was 200 times more active than the W/V extract and 20 times more active than the PNU preparations. The investigators verified Cooke's<sup>51</sup> observation (1933) that the potency of extract solutions varied with the diluent and time and recommended a 50% glycerol solution for the storage of concentrates. Immunotherapy was proposed, rather than the commonly used desensitization, as the most accurate reflection of the changes that take place, observing that although reagin levels did not change much over the course of therapy, blocking antibody levels increased more than 100 times.<sup>71</sup>

Studies from the 1980s to the present reflect the improving pharmacologic alternatives to immunotherapy, with cromolyn commercially available in the late 1970s, second-generation (nonsedating) antihistamines in the early 1980s, and topical steroids without major mucosal or hypothalamic/pituitary suppression in the later 1980s.<sup>7</sup> Hence, immunotherapy for just single-season pollen sensitivities came into question, and allergy organizations adopted verbiage that reflected environmental modification, if feasible, and initiation of pharmacotherapy before resorting to injection therapy. By the time of the study by Durham and colleagues<sup>71</sup> in 1999 on immunotherapy for timothy sensitivity, control subjects were allowed effective pharmacotherapy (with minimal side effects) as a real-world assessment of any added benefits from immunotherapy. This study, a landmark as those mentioned in the prior paragraph, established that after 3 years of immunotherapy, there was

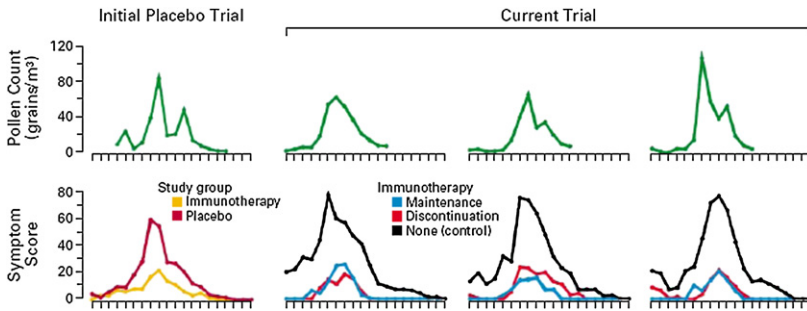


**Fig. 5.** Graphs depicting grass pollen counts over the course of a year (peak counts in summer) in which the placebo group was given subcutaneous saline/histamine and the active group immunotherapy ("initial placebo trial"). Then, after 3 years of immunotherapy, the study extended 3 further years ("current trial") during which those initially given immunotherapy were split into 2 groups, 1 receiving placebo shots and 1 completing 3 more years of immunotherapy (for a total of 6 years). There were no detectable differences between those receiving 3 versus 6 years of immunotherapy, and both groups experienced significantly fewer in-season symptoms than those on medication alone (all groups were permitted rescue medication in season). (From Durham S, Walker S, Varga E, et al. Long term clinical efficacy of grass pollen immunotherapy. *N Engl J Med* 1999;341:471, figure 1; with permission.)

no difference in the symptoms or medication requirements of those whose shots continued for 3 further years versus those who received 3 years of histamine-spiked placebo injections and that both groups did better than control subjects (**Fig. 5**). This study established that 3 years of immunotherapy with adequate levels of major allergen provided long-term benefits (5 years at least, per continuing follow-up of participants) and patients with moderate to severe symptoms from a particular allergen, even if seasonal, could achieve benefit beyond that afforded by pharmacotherapy alone.

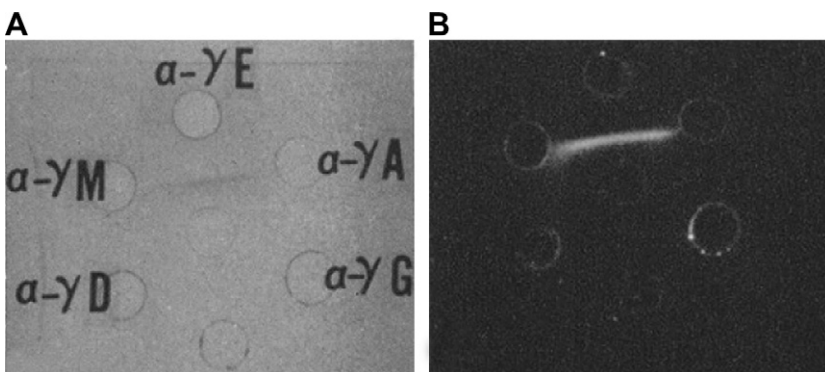


**Fig. 6.** Radioimmunodiffusion analysis of reagin-rich serum from a ragweed-sensitive patient. The serum is in the center well, and around such are arrayed solutions of antibodies specific to each immunoglobulin, including the newly isolated IgE, which had paralleled the concentration of reagin in the patient's serum. Ergo, IgE = reagin, first identified as a marker of inhalant allergies by Coca<sup>46</sup> in 1925. (From Ishizaka K, Ishizaka T. Identification of gamma E antibodies as the carrier of reaginic activity. *J Immunol* 1967;99:1194, figure 5; with permission.)

## ANTIGEN STANDARDIZATION

Durham colleagues' study benefited from progress in allergen standardization, a widely held goal since promulgation of PNU by Cooke and colleagues.<sup>51</sup> Progress had begun in 1959 with the isolation of the key allergenic fraction of house dust by Vannier and Campbell<sup>35</sup> and 3 years later with the identification of antigen E as the major ragweed allergen by King and Norman.<sup>72</sup> In 1967, Voorhorst and colleagues<sup>63</sup> established mite as Vannier's allergen, important in both perennial allergic rhinitis and asthma.<sup>62</sup> Ishizaka and Ishizaka<sup>73</sup> that same year documented reagin to be IgE (**Fig. 6**) and set others on a track, which by 1975 led to the first commercial availability of an allergen-specific IgE immunoassay, although such was not endorsed by the American Medical Association as an alternative to skin testing and a guide to the initial starting dose until 1986.<sup>74</sup> There followed a quest to identify the major allergens of common inhalant sensitizers, thereby allowing extract standardization sufficient for consideration by the US FDA ([www.fda.gov](http://www.fda.gov)). After acceptance of amb 1 as the major allergen in short ragweed in 1975, the major allergen for vespid was endorsed in 1981, cat in 1983, house dust mite in 1990, and many grasses in 1998.<sup>75</sup> At present, 19 allergens are certified for commercial use; however, there are none for molds, cockroach, or many tree or weed pollens or for oral administration (by mid-2009, 4 allergens for oral administration were authorized in Germany but only 1 throughout the European Union).<sup>59</sup> On parallel course, there were dose-ranging studies that have established for standardized allergens the cumulative injected dose that afforded relief in most patients, replacing prior empiric-based strategies with the vaguely characterized end points of a maximum tolerated dose, optimum dose, or symptom-relieving dose.<sup>76–78</sup>

## IN VITRO ALLERGY SCORING AND ALLERGY SCREENS

Practitioners initially struggled to correlate the degree of patient sensitivity as evidenced by skin testing to that of the radioactive counts reported in the early radioallergosorbent assays (now largely replaced by enzyme linked immunosorbent assays, which eschew the handling and storage issues of radioactive tracers). Several scoring systems were proposed. In 1977 Fadel and Nalebuff, modifying the technique with an increased incubation time and other changes, constructed a 6-level scoring system that roughly correlated with a 1:5 intradermal skin titration technique.<sup>79–81</sup> The progressively increasing number of commercially available allergens both for skin (more than 200, most nonstandardized)<sup>59,76</sup> and in vitro testing led to the concept of allergy screens to identify those in a patient suspected of significant inhalant sensitivities, and on which it would be cost-justifiable to proceed with a full battery of tests, usually 20 to 30 allergens deemed likely culprits based on patient history. In 1982 King,<sup>81</sup> and later Nalebuff,<sup>82</sup> documented that a geographically adjusted in vitro screen of 8 to 10 carefully selected allergens was sufficiently efficient to identify more than 90% of those who would have 1 or more major sensitivities detected by a full battery of tests. This cost-effective approach was confirmed by a 2009 Pan-European study (more than 3000 subjects) that confirmed that an 8 to 10 allergen battery of prick tests identified at least 95% of sensitized subjects, and hence the cost to the nationalized health insurance systems of a full test battery could be justified.<sup>83</sup>

## RECENT REVIEWS AND GUIDELINES

The aforementioned advances in extract standardization, specification of effective doses, and the like were supported by increasingly sophisticated laboratory assays. Although Cooke, courtesy of Coca, had a crude assay for reagin in 1925,<sup>44</sup> by 1999,

Durham had sufficient technology to establish per skin biopsy T-cell and interleukin 4 infiltrations at allergen injection sites.<sup>72</sup> Recent investigators have access to a wide gamut of specific T-cell identifiers with their associated cytokines and even some of the genetic switches relevant to allergy and asthma. The reader is referred to recent summaries of this fascinating area, which have allowed clinicians to tie patient responses to serum parameters, adding a further layer of objectivity to many recent trials.<sup>77,84–86</sup> With the earlier-mentioned allergen and laboratory advances, organized allergy again sought to standardize evaluation and treatment methods. Meta-analyses, including a Cochrane Review in 2007, had confirmed that appropriately administered injection immunotherapy (1) improved patient quality of life, (2) diminished medication use and the development of new sensitivities or asthma, and (3) ameliorated nasal, conjunctival, and, to a lesser degree, bronchospastic issues.<sup>78,87–89</sup> A similar review in a 2009 World Allergy Organization position paper on oral immunotherapy reflected much the same, although not as clearly because of a wide heterogeneity of studies, a paucity of standardized allergen preparations for sublingual use, and continuing uncertainties about allergen dosing, administration schedule, and treatment duration.<sup>59,90,91</sup> Recent guidelines by organizations in the United States (2008, injection therapy)<sup>88,89</sup> and Europe (2009, injection and sublingual therapies)<sup>59,90,91</sup> for future clinical trials specify allergens of known potency for which handling and administration must be detailed. Both subjects and practitioners must be blinded as to randomly assigned treatment versus placebo arms, and the investigation must encompass sufficient subjects to power statistically valid conclusions.<sup>92,93</sup> A related initiative is the CREATE project, funded by an agency of the European Union, to construct via recombinant technology the major allergens of common inhalant offenders, the ultimate in allergen standardization and well beyond the current FDA-approved standardized extracts, which although achieving extract purity much better than W/V or PNU, allow for up to a 4 times variation among commercial preparations.<sup>94</sup> Not ready for commercial release, progress has been made with replication of the major allergens of birch and of timothy pollens.

## SUMMARY

This article summarizes the developments that led to the current approach to immunotherapy. These developments were characterized in the early years by empirically derived successive approximations to arrive at effective injection regimens, in the middle years by a sorting through of the wide variations in practice with placebo-controlled clinical trials, and more recently by a closer association of clinical and laboratory measures to better define evidence-based practices. The pace of investigation along with the scientific quality continues to increase. As per a PubMed ([www.pubmed.gov](http://www.pubmed.gov)) search, there were more than 1000 articles on inhalant allergy in 2009. Two entities deserve recognition for the encouragement of, frequently with funding, current pursuits in clinical and bench research that will determine the next article on the understanding of the treatment of inhalant sensitivities. These are the National Institute of Allergy and Infectious Diseases ([www.niaid.gov](http://www.niaid.gov)) within the National Institutes of Health of the United States and the Global Allergy and Asthma Network ([www.ga2len.net](http://www.ga2len.net)) supported by the European Union's Framework Program for Research.

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