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.[1,2] 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,[2] from Galen and others, but it was not until 1891 that Ehrlich[3] 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.[4] 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.[2,5] Skepticism in the scientific community about both disciplines was characterized by an admonition to the society's first journal editor that "immunology is dead."[5]

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[6] 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.[1,7] 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,[8] 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[9] 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[10] 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[11] had successfully conferred passive immune protection to diphtheria in human patients injected with serum containing antitoxin from previously infected animals (usually horse).