



How Allergen Extracts Are Made—From Source Materials to Allergen Extracts

The importance of knowing how allergen extracts are manufactured



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One of the guest editors of this issue, Rosa Codina, PhD, contacted me more than a year ago to suggest that we consider publishing a series of articles about “how allergen extracts are made.” I thought about it and immediately realized that this subject is rarely covered in the repertoire of literature that is ordinarily read by physicians, particularly allergists/immunologists. For example, it is not covered in the 519-page book that Dennis K. Ledford, MD, and I edited entitled *Allergens and Allergen Immunotherapy: Subcutaneous, Sublingual and Oral*.¹ In addition, a 2016 special edition of the journal *Immunology and Allergy Clinics of North America*, entitled *Aeroallergen and Food Immunotherapy*, edited by Linda S. Cox, MD, and Anna H. Nowak-Węgrzyn, MD, does not cover this subject.²

Dr Codina and I agreed that we also should include Robert Esch, PhD, in this endeavor. Both Drs Codina and Esch have considerable experience in the biopharmaceutical industry and expertise in this area.

Acceptance for Publication and Items Included

A good portion of my academic life and the lives of other editors has been devoted to allergens and allergen immunotherapy. Therefore, the 3 of us collaborated and recommended to Gailen Marshall, MD, PhD, Editor of the *Annals of Allergy, Asthma & Immunology*, that we produce this series of articles. He jumped on the idea. Thus, in this special issue of the *Annals*, source materials for pollen, mites, insects, animal danders, fungi, Hymenoptera venoms, and food allergens are discussed by experts. Thus, the whole repertoire of materials used to manufacture allergen extracts, not only for in vitro and in vivo testing but also for use in allergen immunotherapy, is covered. Modified allergens, allergoids, and alum-precipitated extracts are also reviewed. In a look to the future, an article also is included on single recombinant/purified major allergens and peptides and how they are produced. The

expert faculty who volunteered for this project did a tremendous job in contributing to this literature.

Importance

More than not, the science behind the use of allergens for testing and allergen immunotherapy and allergen immunotherapy itself is underrepresented in postgraduate programs and training program curricula. This is indeed unfortunate. It is particularly unfortunate with the advent of new and different forms of immunotherapy (eg, oral, epicutaneous, and sublingual). The knowledge of allergens and how they are manufactured is and will become even more important for different forms of immunotherapy, not only for research but also for appropriate patient care. For example, will the allergens used for oral immunotherapy differ from those used for epicutaneous or sublingual immunotherapy? Which ones will continue to be derived from naturally occurring substances while others are modified or cloned?

Another illustration of the importance of how allergen extracts are manufactured is in the complexity of doing so. Fungal allergens are a great example.³ It is widely recognized that identification of common fungi is difficult and based on the fungal colony characteristics. Microscopic characteristics can vary according to the medium on which a fungus is grown, the incubation temperature, the strain variation, and pleomorphic nature of the spores. Likewise, allergen extracts produced from molds differ, depending on whether the spores, hyphae, or culture filtrates are used to prepare them. This is an area in which a great deal of research should be forthcoming to produce better extracts, in this case fungal extracts, that are consistent batch to batch in their allergen content.

One other point is that many allergens cross-react. Therefore, knowledge about raw materials used to produce allergen extracts will enhance the ability of allergists/immunologists to determine, using the history from the patient and appropriate skin tests or specific IgE in vitro tests, which allergen extracts are most appropriate, and which cross-react, to include in a vaccine. It will also provide knowledge about which allergen extracts contain enzymatic activity and should not to be inappropriately mixed with

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another, unless they are modified or treated to negate this enzymatic activity.⁴

“You’ve Come A Long Way, Baby”

To illustrate how far we have come, to use an old Virginia Slims cigarette ad cliché, “You’ve come a long way, baby.”⁵ During my youth, my brothers and I assisted my father, Stephen D. Lockey, MD, a family physician who ultimately became an allergist/immunologist by apprenticeship, to prepare his own extracts for pollen, animal danders, fungi, and house dust. These extracts were produced from the raw materials that he collected or were available from outside vendors. For example, he would ask a patient to collect house dust from their home and from that dust produce an autologous house dust extract to be used only for that patient. Each autologous house extract theoretically was different and unique for each patient. It made sense.

Source materials were first sonicated, then extracted, concentrated, and sterilized, and eventually used for skin testing and subcutaneous immunotherapy; this was a common practice at the time. Many allergists/immunologists prepared their own extracts before they became universally available via pharmaceutical firms.^{6–9}

Today, colleagues in the pharmaceutical industry produce quality extracts to diagnose and treat allergic diseases. Many are standardized on the basis of biologic or immunologic activity, whereas when I first began in the specialty, in 1968, standardization was limited to the weight by volume (wt/vol) or protein nitrogen units (PNU) system. Similarly, many extracts produced in the past by the pharmaceutical industry are no longer available because they do not meet the US Food and Drug Administration (FDA) current standards for safety and efficacy. The process of the FDA eliminating some of the extracts, not clinically proven to be useful or effective, will continue into the future. Likewise, with the wider use of allergen immunotherapy, by the sublingual, subcutaneous, epicutaneous, and perhaps other routes, the number of standardized allergens will most likely continue to increase. New products also will be forthcoming, which likely will be equally or more effective and even safer.

Allergists/Immunologists First to Use Immunotherapy

The use of allergen immunotherapy began more than 100 years ago. It continues to be a mainstay of treatment for a variety

of allergic diseases, including allergic rhinitis and conjunctivitis, allergic asthma, atopic eczema, and Hymenoptera hypersensitivity. Allergists/immunologists were the first to use immunotherapy, which today also is being used to treat inflammatory and autoimmune diseases and some malignant tumors. The role of immunotherapy in medicine will continue to expand and so, too, will the use of allergen immunotherapy. To do so, extracts that are standardized and safe will be needed well into the future. As time passes, in certain situations, recombinant and modified allergens, and yet to be discovered products, will replace some of the allergens and practices described in this unique series of articles.

Allergists/immunologists can be proud of the fact that they were the first to use immunotherapy to alter the immune system and create immune tolerance.¹⁰ My thanks go to each author of these scholarly articles, again, recommended reading for all physicians interested in our specialty. Appropriate treatment cannot be performed by physicians trained in allergy and immunology unless they are well-versed in the basic fundamentals of how allergen extracts are produced and which ones are best to use to diagnose allergic diseases and treat these patients.

References

- [1] Lockey RF, Ledford DK, eds. *Allergens and Allergen Immunotherapy: Subcutaneous, Sublingual and Oral*. 5th ed. Boca Raton, FL: CRC Press; 2014.
- [2] Nowak-Węgrzyn AH, Cox LS. Aeroallergen and Food Immunotherapy. *Immunol Allergy Clin North Am*. 2016;36:1–214.
- [3] Vijay HM, Kurup VP, Bernstein JA. Fungal allergens. In: Lockey RF, Ledford DK, eds. *Allergens and Allergen Immunotherapy: Subcutaneous, Sublingual and Oral*. 5th ed. Boca Raton, FL: CRC Press; 2014: 163–179.
- [4] Esch RE. Allergen immunotherapy: what can and cannot be mixed? *J Allergy Clin Immunol*. 2008;122:659–660.
- [5] Virginia Slims. https://en.wikipedia.org/wiki/Virginia_Slims. Accessed February 15, 2016.
- [6] Vaughan WT, Black JH. *Practice of Allergy*. 2nd ed. St Louis, MO: CV Mosby Co; 1948.
- [7] Feinberg SM. *Allergy in Practice*. 2nd ed. Chicago, IL: The Year Book Publishers Inc; 1946.
- [8] Unger L. *Bronchial Asthma*. Springfield, IL: Charles C. Thomas; 1945.
- [9] Tuft L. *Clinical Allergy*. Philadelphia, PA: Lea & Febiger; 1949.
- [10] Lockey RF. Historical perspectives of allergy and immunology and allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2014;113: 587–592.