

Historical Perspectives and Current Standards of Immunotherapy: Challenges and Unmet Needs

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At the end of this lecture, participants will better understand:

1. the history of allergen immunotherapy,
2. how the last 50 years of research have led to current day standards of care resulting in increased efficacy, safety, and new modes of allergen immunotherapy, and
3. understand the challenges to develop an ideal form of allergen immunotherapy which is safe and can be used to prevent and treat allergic diseases.

Personal Note: The following is a personal recollection of my lifetime interest in allergen immunotherapy.

During my youth, I was first exposed to the specialty of allergy while assisting my physician-father in preparing allergen extracts, now referred to as allergen vaccines, for his clinical practice in Lancaster, Pennsylvania, U.S.A. This was prior to the time that many commercial extracts were available for widespread use. He was trained as a family practitioner and later, following the Second World War, took an apprenticeship in allergy at the University of Pennsylvania, Philadelphia, Pennsylvania. Training in allergy and immunology was not formalized at that time. Thereafter, he devoted his entire life to the field. Figure 1 is a picture of my father and his charge nurse in the early 1950s.

Early in life, I always wanted to become a physician which resulted in attending a college which prepared me for this profession. While in college, I had the privilege of participating in immunologic research in a basic laboratory and became fascinated with the world of immunology, an area of special interest to two of my professors. I vividly remember plating out Petri plates with agar gel, cutting and aspirating the wells,

and then applying antigen and serum containing antibodies for Ouchterlony double-diffusion studies. Likewise, similar studies to identify antigen-antibody reactions were carried out in capillary tubes. I also remember how disappointing it was when my roommate's name was included on an abstract on the research we were doing. Mine was not. The professor informed me that in order to have your name included on an abstract or paper, one had to contribute to the research, not just the technical work.

After admission to medical school, we, of course, spent the first two years trying to learn a second language and the complexity of medicine. During this time, we had clinical lectures about allergy/immunology, and I remember how fascinating it was to observe skin test reactions, both immediate and delayed, as well as understanding 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 in medical school and during my internship was mentored by the late Dr. Felix Cortes, a professor of pulmonology at Temple University School of Medicine, Philadelphia, and later Chief of Medicine at Ponce Medical School, Puerto Rico. He involved me in a project to study blood gases in acute asthmatics as they reported to the emergency room. The standard-of-care at the time was to give them morphine sulfate, demerol, or phenobarbital as part of their emergent treatment. We performed some of the first studies which demonstrated severe blood gas abnormalities. Many of these patients were hypoxemic with severe acidosis or alkalosis. When this knowledge became known to the medical community, these practices were curtailed and quickly discontinued. These results were extremely impressive to me because of the inappropriate and widely accepted use of such medications to allegedly relieve the anxiety in patients with severe respiratory distress. Of course, the anxiety was not the problem, the respiratory distress was the problem.

About this same time, in the mid-50s and early-60s, different double-blind controlled studies with subcutaneous allergen immunotherapy illustrated its effectiveness. However, optimal doses were not defined, extracts were not standardized, and there were no practice parameters available or universal

guidelines for administering such therapy and adverse reactions were occurring, some fatal, which were either underreported or reported as simple case reports.

After my training was completed in internal medicine, a residency in allergy and immunology came next. The contents of our training were based primarily on clinical impressions rather than evidence-based medicine. A book, entitled *A Manual of Clinical Allergy* utilized in our training program, was 550 pages and written by our faculty, 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 (Figure 2) Contrast this book with Middleton's *Allergy: Principles and Practice*, 7th edition, which is 1800 pages During training and while in graduate school, blood group antigens became my area of interest. Working in the 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. Aspirin-exacerbated asthma was also an area of interest and, with the help of Dr. Neil Vanselow, we were able to demonstrate a genetic link for this syndrome. I was fascinated with the fact that "experiments in nature", as so often quoted by the late Dr. Robert A. Good, could result in translational research to benefit medical science.

Thereafter, the US Air Force called with the privilege of supervising an allergy/immunology clinic at a large Air Force base hospital in Texas. Young active duty service members and their families and many retirees were the patients cared for in this clinic. This experience confirmed my impression that many of the things that we did in medicine and, in particular, in our specialty, were simply based on clinical impressions with few well-designed scientific-based studies. This also was true of subcutaneous immunotherapy which had evolved with time based primarily on clinical impressions, not on adequately designed scientific studies. During this time in the Air Force, I also had the privilege of working with Dr. Raymond Zeiss. Together, we were able to do clinical studies with aspirin-exacerbated asthma demonstrating that desensitization was possible in such patients. This clinical paradox fascinated us and was instrumental in both of us entering academic medicine. Dr. Zeiss later became a faculty member and professor at Northwestern University in Chicago.

Just think, the main treatment for asthma in the early 1970s was a combination of some or all of the following medications: phenobarbital, aminophylline, and hydroxyzine hydrochloride or ephedrine. Inhaled isoproterenol was the mainstay for acute asthma. Many patients later died in certain countries of the world from excessive use of this medication. I remember transporting asthmatic patients in acute distress to the operating room to give them general anesthesia with ether, which caused bronchodilatation, as well as to intubate them. Likewise, we sometimes gave patients ipecac to make them vomit, inducing a vagal response, which sometimes caused improvement. Epinephrine was a mainstay of treatment for asthma, i.e., 0.5 mg q 20 minutes x 3. Systemic glucocorticosteroids were available, however, while they already were “wonder drugs”, they quickly became associated with major side effects because they commonly were over-utilized and, in general, given in excessive doses. For years, there was a reluctance to use them because of their serious side effects. Theophylline toxicity also was a common occurrence. Hospitalization for severe asthma was the rule rather than the exception and intubation and assisted ventilation not an unusual supportive procedure. The water-sealed Jones spirometer (Figure 3) and the piston-driven Emerson Ventilator were the standards-of-care.

After my two-year stint in the U.S. Air Force, in 1973 I joined the late Dr. Samuel Bukantz my mentor at the University of South Florida, Tampa, Florida, where we had many conversations about the specialty of allergy and immunology and, in particular, about subcutaneous immunotherapy and the lack of adequate science and guidelines. Both of us felt it was an important form of therapy but lacked good evidence for efficacy and safety. Systemic allergic reactions were fairly common in our clinics in which we worked.

Several years before moving to Florida, I had already joined the American Academy of Allergy, now the American Academy of Allergy, Asthma & Immunology, and became a member of the Committee on Insects. In 1979, the work by Hunt, Lichtenstein et al., from Johns Hopkins University, Baltimore, indicated that venom immunotherapy, versus venom extracts, was effective to treat venom hypersensitivity as previously illustrated by the late Dr. Mary Loveless in non-controlled studies. One of

the members of the Committee, Dr. Paul Turkeltaub, was also a staff member of the Federal Drug Administration (FDA) in Washington, DC. At his urging, the Hymenoptera venom studies were organized under the auspices of the Committee on Insects. These were Phase IV studies, encouraged by the FDA, to determine whether or not venom immunotherapy was safe, in particular, when used for many consecutive years. This resulted in a variety of different publications which indicated that treating stinging insect anaphylaxis was safe as long as the appropriate guidelines, as mandated by the FDA, were followed (1). Likewise, there were no major long-term side effects. The use of standardized venom vaccines for venom immunotherapy to treat Hymenoptera hypersensitivity was a hallmark for our specialty: first, because it demonstrated that venoms versus whole body extracts were effective; second, because standardized venom vaccines became available and were safe; and third, because of the demonstrable immunologic changes that occurred associated with such therapy. It is interesting to note that no deaths have been reported from such therapy since its inception.

About the 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 1982 (Figure 4). A 13-page chapter, written by the late Dr. Roy Patterson and Dr. Phil Norman, and the late Dr. Thomas Van Metre, devoted approximately two pages of the *Primer* to allergen immunotherapy (2). This is one of the first major publications about this subject in the United States, published in a journal read by physicians throughout the world. This *Primer* was also a landmark publication for the specialty for it was a 174-page treatise on the specialty of allergy and immunology written by over 100 physicians and scientists.

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 devoted entirely to "Immunotherapy With Allergens" (3). Again, the evolutionary acceptance of allergen immunotherapy was becoming more widespread. Two other *Primers*

were published subsequently, the last one in 1997, edited by Dr. James R. Baker. All *Primers* were published in many languages throughout the world. The specialty of allergy and immunology had arrived!

Again, working with FDA colleague, Dr. Paul Turkeltaub, deaths from allergen immunotherapy were also being reported in the United States, especially in the latter half of the 20th century. This resulted in a second major undertaking, again, encouraged by the FDA and under the auspices of the American Academy of Allergy, Asthma & Immunology. A survey of allergists/immunologists who practiced in North America was devised to determine the number of fatalities that occurred associated with subcutaneous immunotherapy. This survey, which began in 1983, continues to this day. We reported on 46 deaths, 6 from skin testing, and 40 from immunotherapy. This report was published in the *Journal of Allergy and Clinical Immunology* at about the same time as a report was issued from Great Britain's Committee on Safety reporting an additional 26 fatalities in Great Britain.

These reports were sentinel, because they indicated that subcutaneous immunotherapy, while efficacious, was not safe, in fact, it was associated with deaths. It was followed by several others and gave more impetus to the FDA to standardize allergen vaccines and better regulate their manufacturing process and the means by which they are utilized by physicians to care for allergic patients. At the same time, discussions began within the Academy and, in particular, members of the Committee on Immunotherapy, to begin to develop immunotherapy guidelines, which have now evolved into Practice Parameters, not only in the United States, but throughout the world. Dr. Peter Creticos and I, along with Drs. Bukantz, Ownby, Portnoy, Turkeltaub and Weber, developed the first Practice Parameters on subcutaneous immunotherapy entitled *Immunotherapy: A Practical Guide to Current Procedures* (Figure 5). 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* are reissued every 3 to 5 years in the United States on this same subjects and are much more extensive, covering every aspect of the appropriate manner by which this

form of therapy should be prescribed and administered (4). It is interesting to note only one death in the United States has been reported associated with subcutaneous immunotherapy since 2007. I like to think that the decrease in the number of deaths is a result, at least in part, of the dedication of so many to improve this form of therapy.

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

As the international exchange of information became more and 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 to issue a World Health Organization treatise on allergen immunotherapy. A committee was formed, chaired by Drs. Bousquet, Malling and myself. With 19 colleagues, over a period of a year or so, a document, entitled "WHO Position Paper: Allergen immunotherapy: therapeutic vaccines for allergic diseases" was constructed and, thereafter, distributed throughout the world (Figure 6). This scientific document, for the first time, placed allergen immunotherapy "on the global map", and resulted in a much wider acceptance of its use, not only among allergists/immunologists, but also among all physicians. Of interest, the efficacy and safety of sublingual immunotherapy was mentioned for the first time in this publication.

Since 1998, sublingual immunotherapy has become a re-invented form of immunotherapy and is widely used in various parts of Europe and in other parts of the world. This form of therapy had been utilized in the United States and elsewhere for many years, however, using suboptimal doses, shown not to be

effective. Just as optimal doses are necessary for efficacy of subcutaneous immunotherapy so, too, are such doses necessary for sublingual immunotherapy. Today, there are properly configured powered studies which indicate unequivocally that such therapy is effective and safe. Likewise, the immunologic changes associated with subcutaneous immunotherapy also have been demonstrated with sublingual immunotherapy. Many different investigators have played a role in investigating this new form of therapy. One of the most important documents published on this subject is the World Allergy Organization document entitled *Sublingual Immunotherapy: WAO Position Paper 2009*. Dr. Walter Canonica, along with other colleagues, was instrumental in publishing this very important document (5).

Now, new forms of allergen immunotherapy are being investigated such as intralymphatic and epicutaneous allergen immunotherapy. In addition, a variety of recombinant and modified vaccine adjuvants are being used or developed. Such innovations include recombinant vaccines, genetically-modified recombinant vaccines, recombinant wild-type vaccines, TLR-9 agonists, TLR-4 agonists, allergoids and peptides. The first edition of the book entitled *Allergen Immunotherapy*, edited by Dr. Bukantz and me, consists of 13 chapters (Figure 7). The newest edition, to be published in 2014 and edited by Drs. Dennis K. Ledford and me, consists of 38 chapters, illustrating how this form of therapy to treat allergic diseases has evolved (Figure 8).

Allergen immunotherapy has been utilized to treat allergic diseases for the past 100 years or more and will continue to be utilized, not only to treat allergic diseases, but ultimately to prevent them. Various other forms of immunotherapy are also being used today to treat autoimmune and oncological diseases. Vaccines of all kinds will continue to be developed to augment the immune response and to create immunologic tolerance.

Allergists/immunologists can be very proud of the tradition of first using immunotherapy to modify the immune response and to create tolerance to allergens which cause allergic diseases. Again, our specialty

was the first of all specialties to do so. Today, the term “immunotherapy” not only applies to allergen immunotherapy, but other forms of immunotherapy. Likewise, the term “allergen extract” has been largely replaced by the term “vaccine” because today vaccines are not only used to treat infectious disease, but also to treat allergy, autoimmunity, and cancer.

In conclusion, my personal observations and experiences with allergen immunotherapy are unique in that they transcend my entire lifetime. This lecture is not just about my personal experiences with allergen immunotherapy and the studies and initiatives that I have had the privilege to be involved in, but also about the colleagues that I have had the privilege of working with, who have helped to transform a form of therapy which evolved clinically, with little science, to a scientifically-based treatment modality. It also has become a much safer form of immunotherapy. Many of the individuals who are responsible for current day advances are present at this conference.

Many other physicians and scientists before us have been instrumental in passing this tradition forward in our specialty. We owe a great deal of gratitude to them. The specialty of allergy, particularly, allergen immunotherapy, is on solid grounds and will continue to be employed to prevent and treat allergic diseases. I am very grateful for all the varied experiences that helped to make such therapy safer, more effective, and more widely used throughout the world to treat patients with allergic diseases.

Thank you.

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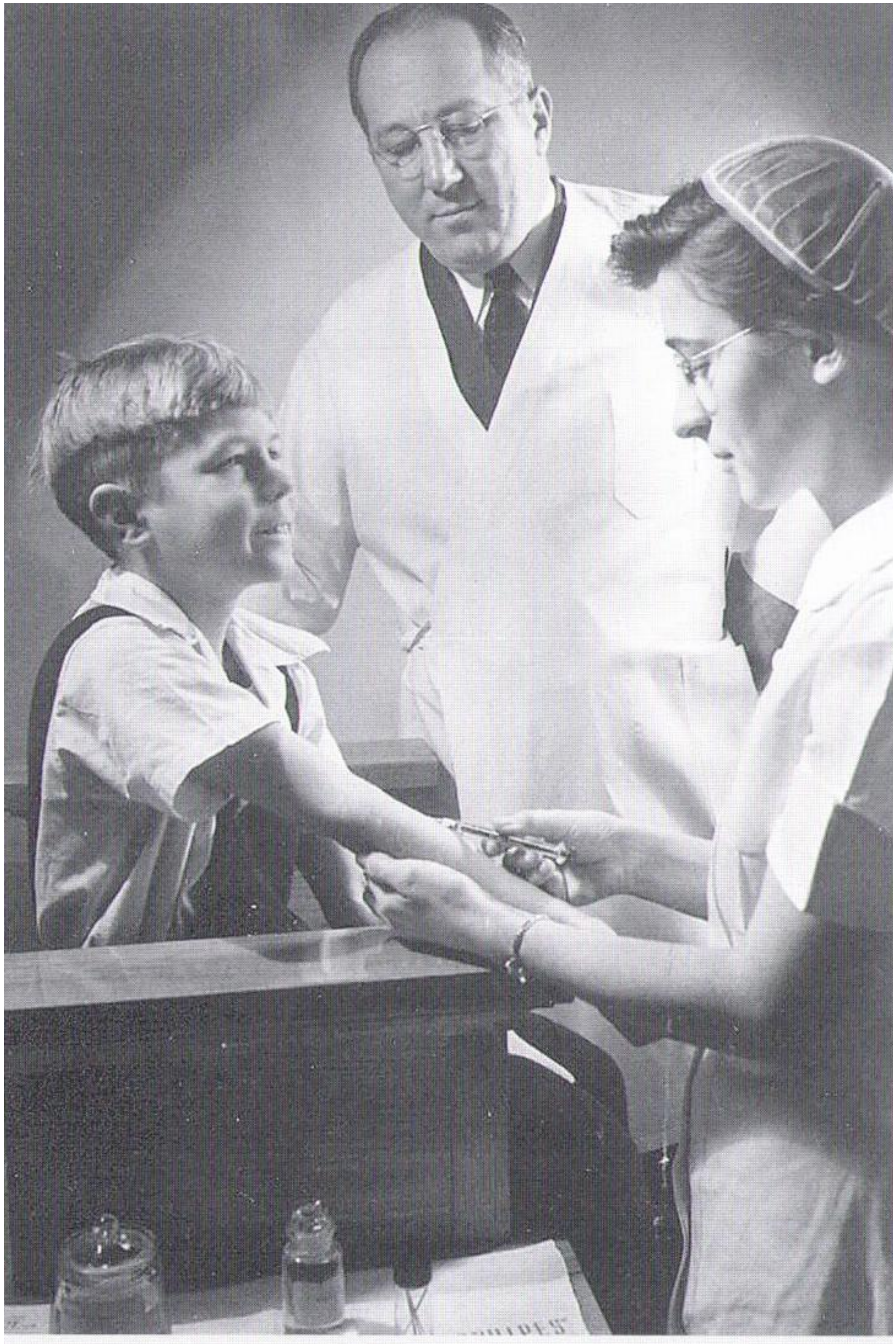


Figure 1

Stephen D. Lockey, Sr., M.D. and his charge nurse, Ms. Sarah Landis (early 1950s).

Lancaster County Historical Society, *Lancaster at Work: Business in Lancaster County, Pennsylvania*.
Lancaster County Historical Society, Lancaster, Pennsylvania, 2006.

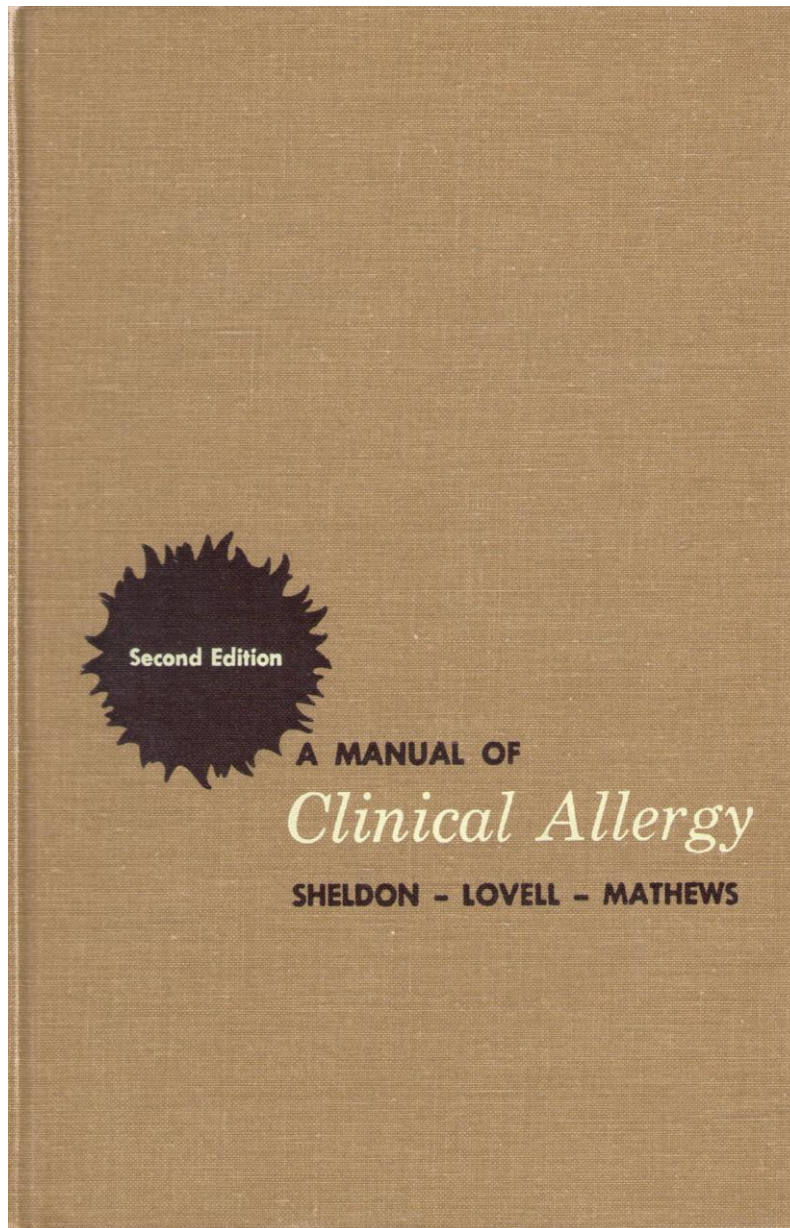


Figure 2

Sheldon JM, Lovell RG, Mathews KP, eds. *A Manual of Clinical Allergy*. Second Edition. W.B. Saunders Company, Philadelphia and London, 1967, 555 pages, 20 chapters.

Contrast this with Middleton's *Allergy: Principles and Practice*, 7th edition, 1800 pages and 97 chapters, 2009.

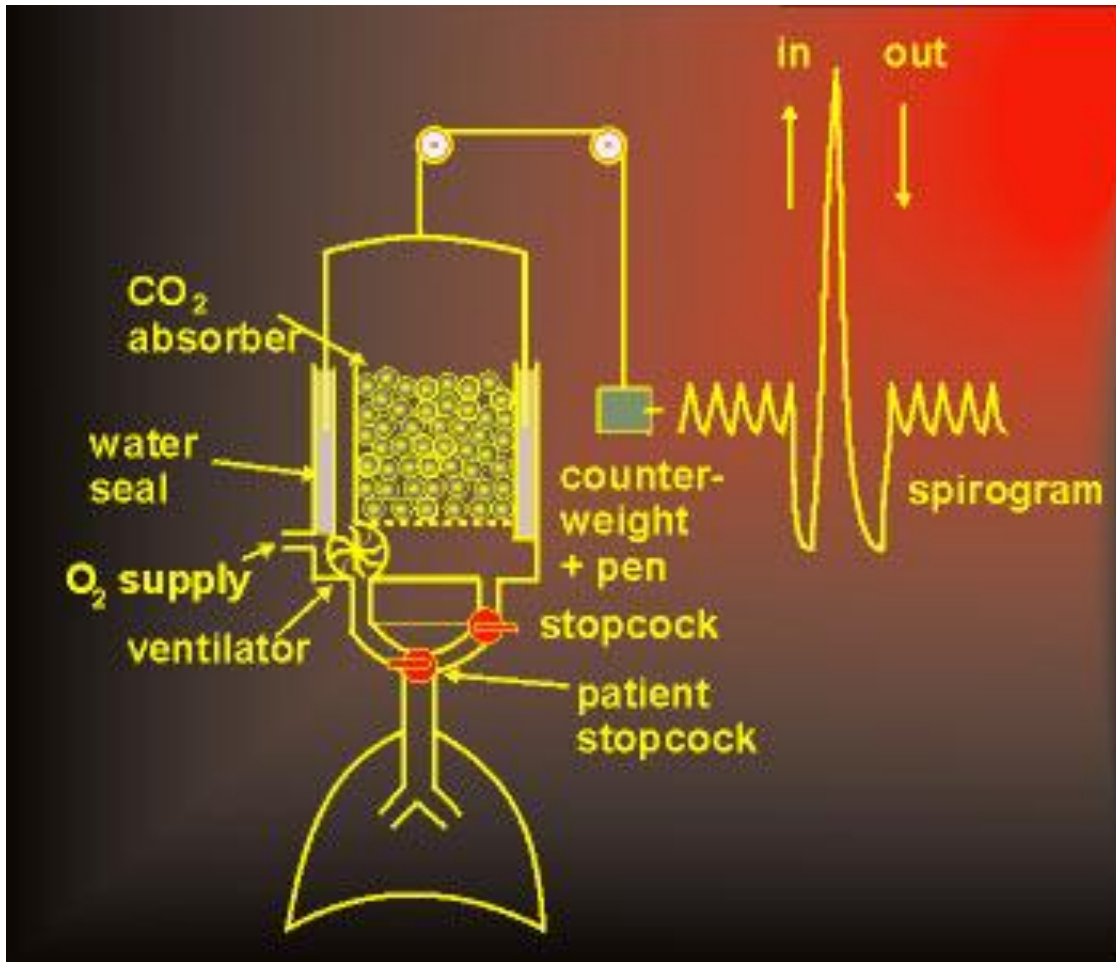


Figure 3

Water-sealed spirometer

<http://www.spirxpert.com/technical6.htm>, October 28, 2013

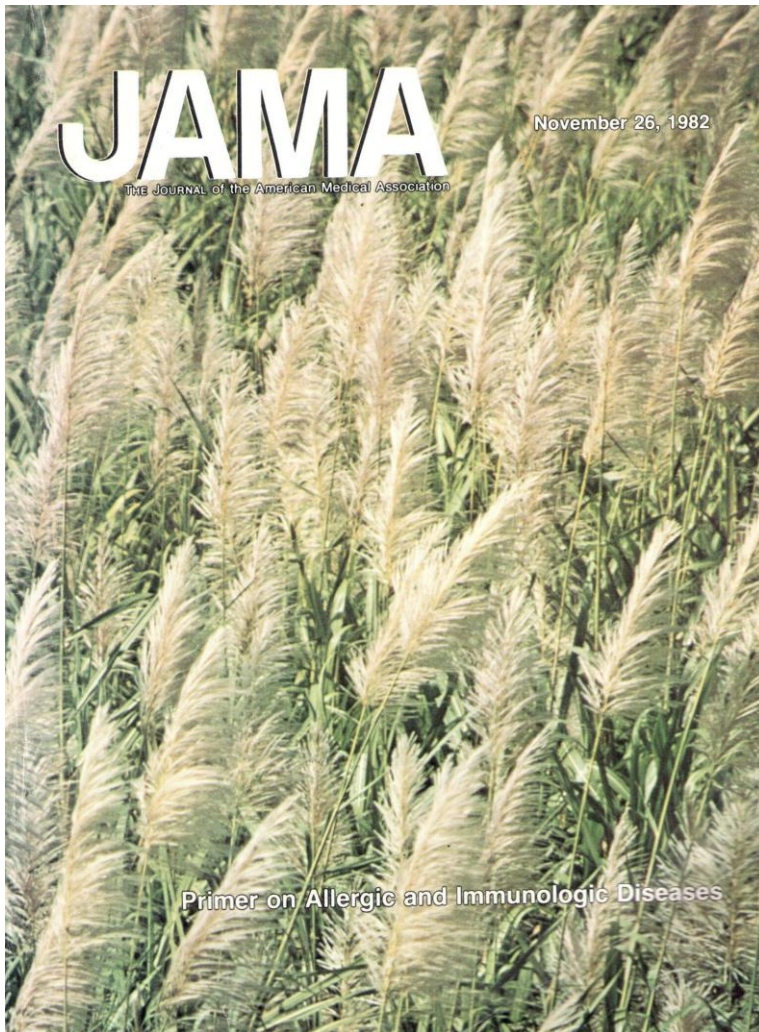


Figure 4

Salvaggio JE (Editor). *JAMA Primer on Allergic and Immunologic Diseases*. American Medical Association. *JAMA* 1982;248(20). First *Primer*, sentinel issue. This *Primer* was followed by three others, 1987, 1992, and 1998.

IMMUNOTHERAPY

A Practical Guide to Current Procedures

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Figure 5

Creticos PS (Editor). Lockey RF (Associate Editor). Bukantz SC, Ownby DR, Portnoy JM, Turkeltaub PC, Weber RW (Contributors). Immunotherapy: A Practical Guide to Current Procedures. American Academy of Allergy, Asthma & Immunology, 1994.

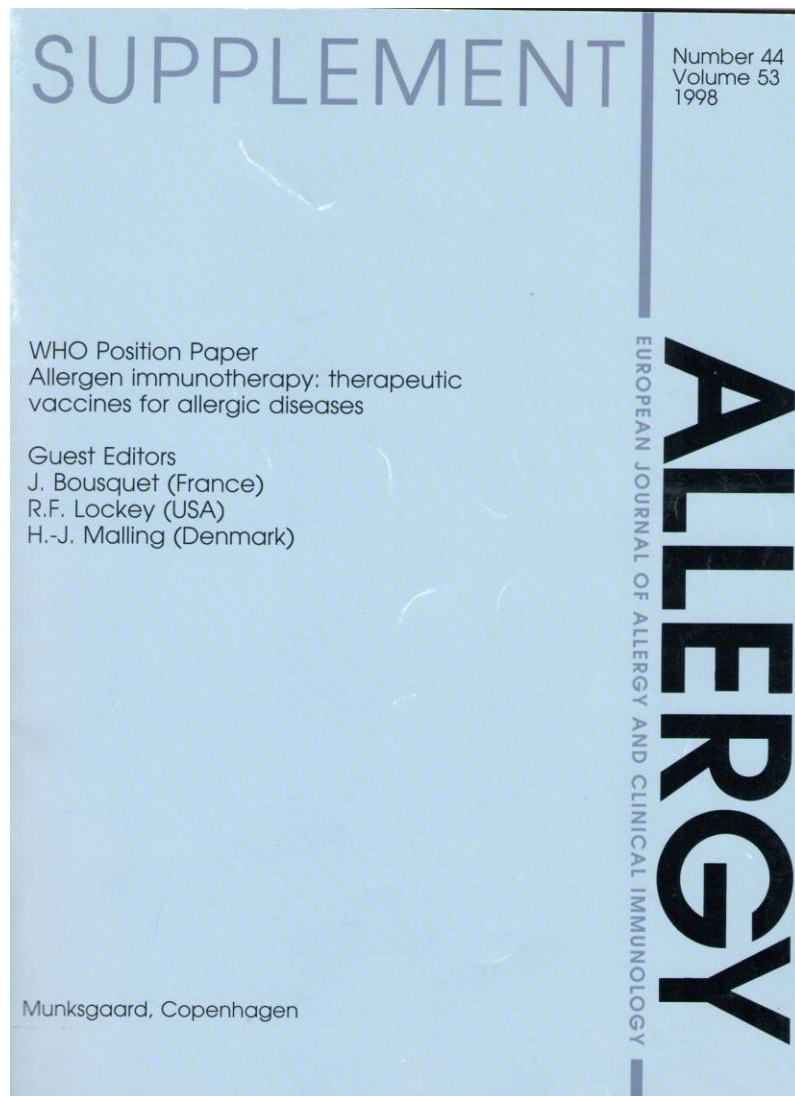


Figure 6

Bousquet J, Lockey RF, Malling H-J. *WHO Position Paper: Allergen Immunotherapy: therapeutic vaccines for allergic diseases.* *Allergy* 1998;44(53):1-42.

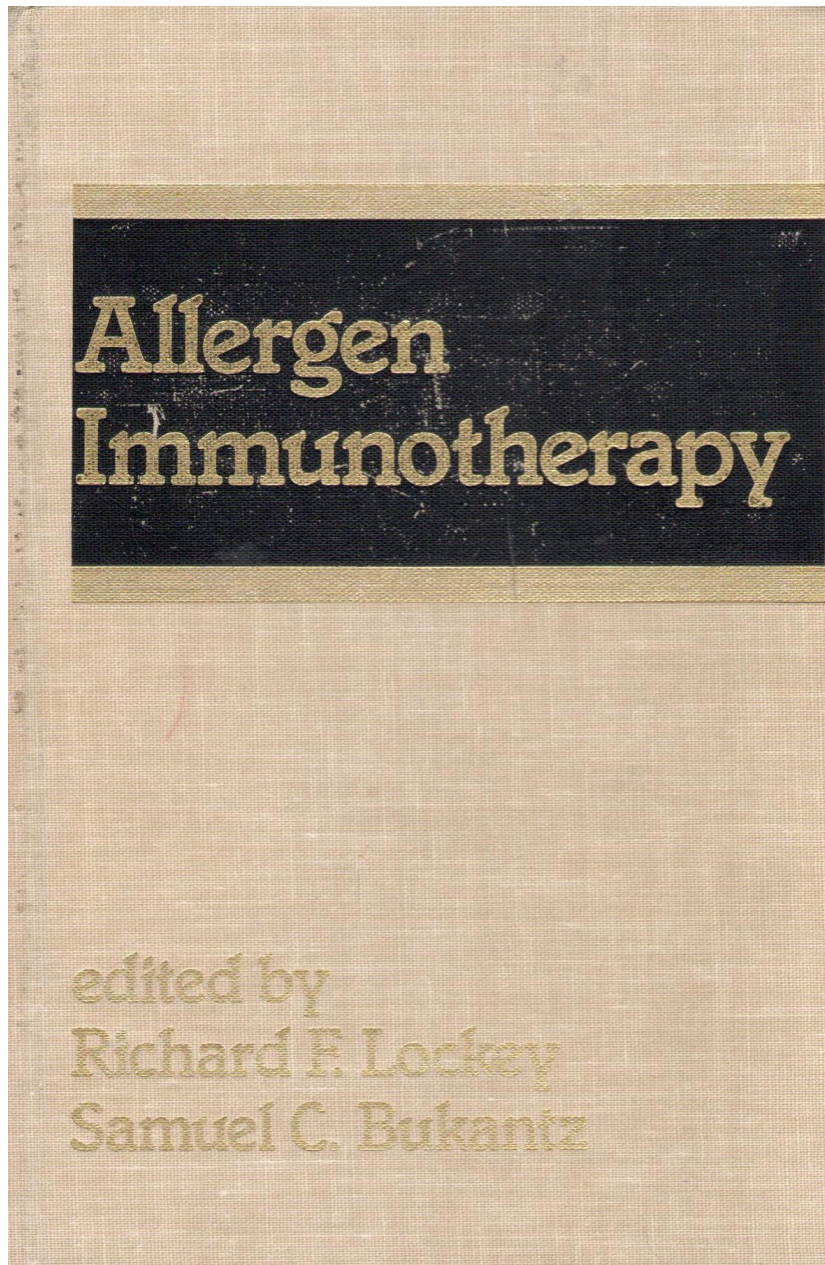


Figure 7

Lockey RF and Bukantz SC, eds. *Allergen Immunotherapy*. Marcel Dekker, Inc., New York, 1991. Contains 13 chapters.

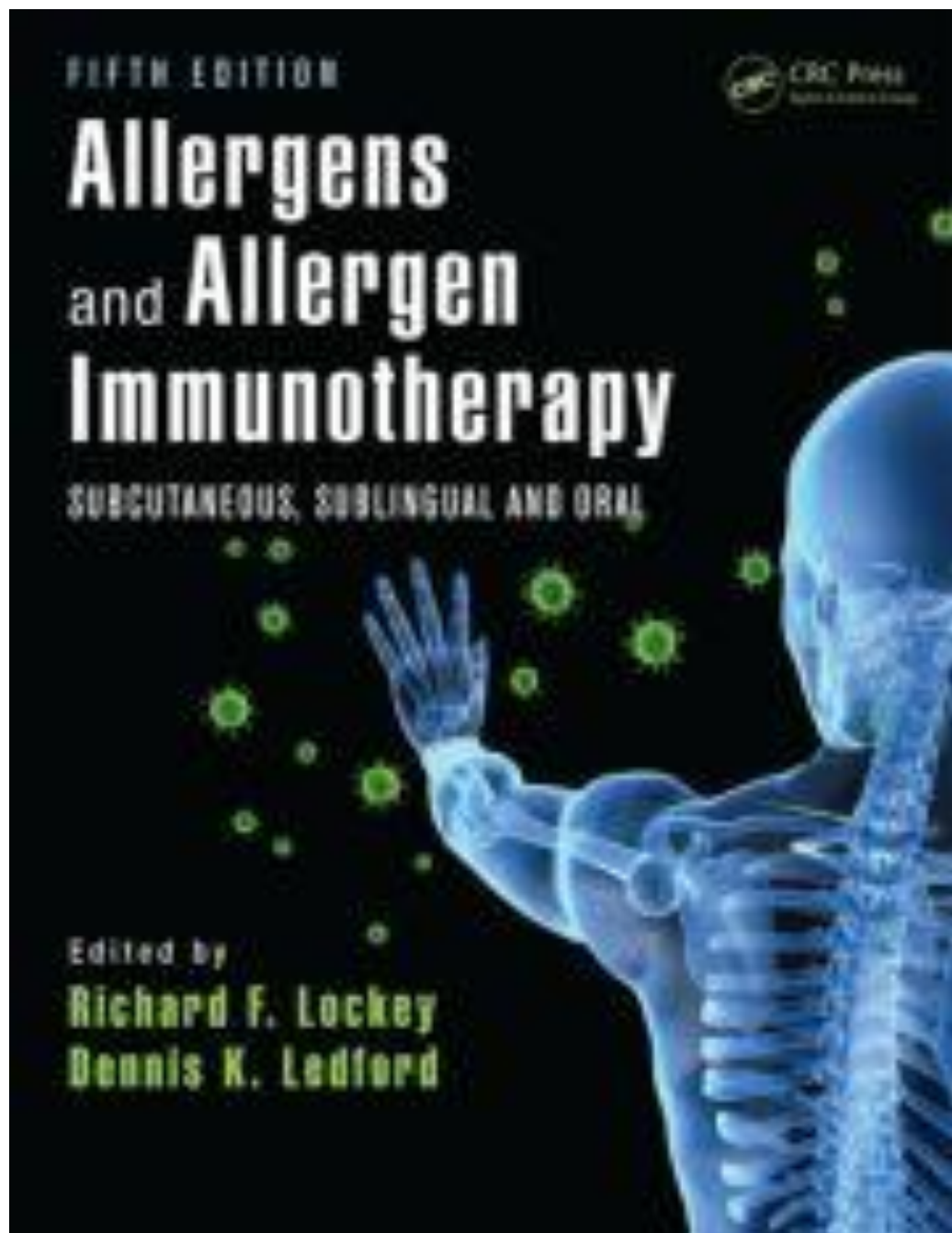


Figure 8

Lockey RF and Ledford DK (eds). Allergens and Allergen Immunotherapy: Subcutaneous, Sublingual and Oral, 5th Edition. CRC Press (Taylor & Francis Group), February 20, 2014. Contains 37 chapters.