

The ALLERGY ARCHIVES

Pioneers and Milestones

Sheldon Cohen, MD, Editor

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Philip S. Norman and Lawrence M. Lichtenstein:
The science of immunotherapy

DYNAMIC DUO: NORMAN AND LICHTENSTEIN AT HOPKINS—HOW IT ALL BEGAN

From the mid 1950s through the 1960s, immunology and allergy were advancing rapidly. Protein fractionation and new serologic and immunologic techniques were being developed. Immune cells and their functions were being identified. Antibodies were identified as immunoglobulins, and were purified and characterized. Immunoglobulin classes were named and their origin and functions identified, with “skin sensitizing antibody” finally identified as IgE in 1967. Allergens were beginning to be purified. Mechanisms of what was then called “immediate hypersensitivity” were being studied *in vitro*. And controlled clinical trials of “desensitization” therapy for allergic diseases, used clinically for half a century, were being undertaken for the first time. It was during this period that what is now known as the Division of Allergy and Clinical Immunology of the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital was being formed within the Department of Medicine. Here is how we saw it emerge.

Although a separate division of Clinical Immunology did not actually come into existence until 1970, its roots were already being formed in the mid-1950s. Philip S. Norman had graduated from the Washington University Medical School and had completed an internship at Barnes Hospital, then a medical residency at Vanderbilt Medical School, followed by 2 years in Merrill Chase’s laboratory at the Rockefeller Institute. He came to Hopkins in 1956 as an Instructor in the Department of Medicine’s Division of Infectious Diseases, which then became the Division of Allergy and Infectious Diseases. He continued his research on the plasmin system and, at the same time, began seeing patients in the Hopkins Hospital Allergy Clinic.

In the early 1960s Phil began to purify ragweed pollen allergens. His first publication, with Don McKaba, appeared in *The Journal of Allergy* in 1962 (33:18-25) and the second, with T. P. King of the Rockefeller Institute, in *Biochemistry* the same year (1:709-20).

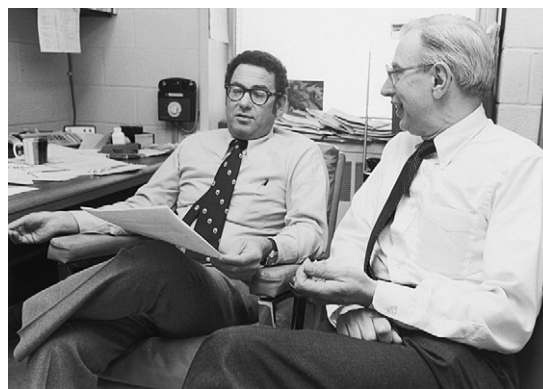


FIG 1. Larry and Phil in the late 1960s.

T. P. King would become Phil’s life-long collaborator in studies of pollen and venom allergens.

In 1961, Phil was named Associate Physician in charge of the Hopkins Allergy Clinic. The Allergy Service at Hopkins had previously been directed by Walter Winkenwerder, who had a large private practice as well, shared with his partner Tom van Metre, Jr, who attended clinic regularly along with other part time attending allergists. Winkenwerder was an ardent clinical researcher who had served as President of the American Academy of Allergy in 1949, as van Metre was to do in 1978. During the ensuing decade, Phil, with his colleagues, initiated what we might consider the first series of modern clinical investigations of immunotherapy using an allergen-standardized extract.

That same year of 1961, Larry Lichtenstein, who had just finished his internship on the Osler Medical Service of the Hopkins Hospital, entered a PhD program across the street in the Department of Microbiology with the immunologist Abraham Osler as his preceptor. What an environment that was: Barry Wood, the Director of the Department, was studying leukocyte migration; Manfred Mayer, whose laboratory was just down the hall from Osler’s lab, was the author of the well known immunology textbook, Kabat and Mayer’s *Experimental Immunochemistry*, and a specialist on complement; and Dan Nathans and Ham Smith were doing their work on restriction enzymes that led to a Nobel Prize in 1978.

Larry had received his MD at the University of Chicago in 1960. While there, he had spent time in the laboratories of 2 outstanding immunologists, Taliaferro and Talmadge. Osler’s research interest was centered around complement and immediate hypersensitivity—in particular, anaphylatoxins. Larry’s PhD research problem was to investigate allergen-induced *in vitro* histamine release from human leukocytes. One of his early observations was that *in vitro* histamine release was not affected by cigar ashes. As is now well known, the results of his research have led to a much better understanding of the mechanisms of this IgE-dependent process, one that is the initiating event

in acute allergic reactions. It also began Larry's life-long passion for the role of the human basophil in allergy and inflammation. This work resulted in several seminal papers and was the basis for his PhD, which he received from Johns Hopkins in 1965. One of us (D.A.L.) became a postdoctoral fellow in Abe Osler's lab in 1962, where he used the human leukocyte-histamine release system to measure human reaginic antibody and thus became well acquainted with Larry's early work.

During his years as a postdoctoral fellow, Larry also took his turn seeing patients in the Hopkins Allergy Clinic, an experience that allowed him to become a clinical allergist. To round out his clinical training, after receiving his PhD, he spent the following year as Assistant Resident on the Osler Medical Service. After morning rounds, he would return to his lab on Blalock 10 to plan the day's experiments, which were usually performed by his first technician, Anne Kagey-Sobotka, who later earned her own PhD under Larry's mentorship. Many Hopkins medical students opted to work in Larry's laboratory during free quarters and summers, including one of us (N.F.A.) who began projects on penicillin allergy which continued into his Osler medical residency.

It was during his years in Osler's lab (1961-1965) that Larry began to collaborate with Phil Norman. Their first study together applied the use of the *in vitro* basophil histamine release model to quantify sensitivity and response to specific immunotherapy with a standardized ragweed extract. This landmark study was published in 1966 in *The Journal of Clinical Investigation* (45:1126-36), more than a year ahead of the Ishizakas' classic *Journal of Immunology* article identifying "reagin" as IgE. Norman and Winkler organized the clinical trial, and Lichtenstein and Osler did the laboratory assessments of immunologic sensitivity. Three additional clinical papers by this pioneering team, all published in 1968, reported on the results of a controlled study of immunotherapy for ragweed hay fever, the value of adjuvants in boosting IgG antibody responses, and a comparison of treatment with "antigen E" (now Amb a 1), the principal ragweed allergen in whole ragweed extract. In 1969, Larry and Phil wrote a review article for *The American Journal of Medicine* (46:163-73) summarizing their work and view of human allergic reactions at that time.

Phil and Larry would go on in the 1970s to preside jointly over a separate Division of Clinical Immunology that would be housed in the newly built O'Neill Research Laboratories at the affiliated Good Samaritan Hospital across town. At the same time, Kimishige and Teruko Ishizaka were recruited from Denver where they had "discovered" IgE. This was followed by a long lineage of recruits and retained trainees that now constitutes one of the world's largest faculties devoted to the study of allergic diseases. In 1989, the Division moved to the new Johns Hopkins Asthma and Allergy Center, where the Norman and Lichtenstein legacy continues to this day.

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LEGENDS IN ALLERGY: PHILIP S. NORMAN AND LAWRENCE M. LICHTENSTEIN—THE HOPKINS EXPERIENCE

Dr Philip Norman began his medical career at Washington University School of Medicine in St Louis, Mo, where he graduated *cum laude* in 1951. During his formative years in medical school, he gravitated toward the emerging field of immunology and has remained in its forefront ever since, through his endeavors in allergen characterization, allergen immunoassays, allergen provocation, and clinical trial design.

After completing his internship the following year, at Barnes Hospital in St Louis, and subsequently his residency in 1954, at Vanderbilt University in Nashville, he received a highly sought after fellowship in New York at the Rockefeller Institute for Medical Research, under Dr Merrill Chase. It was here that he first explored allergen characterization in the laboratory with Dr T. P. King, an association that led to several important publications on the principle protein allergens isolated from ragweed.¹⁻⁴

He was initiated into the Hopkins community in 1956, becoming an Assistant Professor in 1959, and subsequently an Associate Professor in 1964. He was asked to establish a formal Division of Clinical Immunology in 1970. During these early years, he assembled a core team composed of Lawrence Lichtenstein, Martin Valentine, and David Marsh, and began to focus on the underlying pathophysiology and treatment of allergic respiratory disease. The nucleus of this team expanded through the 1970s with the addition of Thomas Van Metre, N. F. Adkinson Jr, and Anne Kagey-Sabotka. The Division grew rapidly in the 1980s as Robert Schleimer, Don McGlashan, Robert Naclerio, Stephen Peters, Edward Schulman, and Peter Creticos completed their fellowships and immersed themselves in the limited confines of the Howard Hughes Institute at the Good Samaritan Hospital, within which the incubating Division began to flourish.

As codirectors of the Division of Clinical Immunology, Drs Norman and Lichtenstein envisioned the establishment of a center to meet the national demand for advances in treating allergies, asthma, and related respiratory disorders. In 1989, the culmination of their

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