

Giants in Allergy–Immunology

Mary Hewitt Loveless, MD

The origin of venom immunotherapy

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If ever there were an allergist whom I wish I had the chance to meet, it was Mary Hewitt Loveless, MD. Regrettably, I didn't, and so my sources for this remembrance are secondhand. Yet the legacy of this truly original investigator continues to grow, now 27 years after her death, at age 92, on June 2, 1991.

In selecting material for this brief narrative, I have relied on the reports of 2 authorities in the field of allergy: Sheldon G. Cohen, MD (Editor of *The Allergy Archives* when he published his thoughts about Loveless,¹ some of which were derived from his eulogy delivered at her memorial service at the Saugatuck Congregational Church in Westport, CT, on June 22, 1991) and Martin D. Valentine, MD (of Johns Hopkins University School of Medicine²). I highly recommend these 2 articles for those who wish to gain a better familiarity with Dr. Loveless's career and contributions than is possible based on this short article.

Mary Hewitt was born in 1899 in Clovis, California, to members of prominent British families who left England in the hope of escaping economic depression.¹ Without significant means, Mary worked part time (as a waitress, clerk, or secretary) while enrolled at Stanford, receiving her BA degree in 1921.¹ Dr. Cohen wrote¹ that “she was remembered as bright, exquisitely attractive, tall and slender, with striking blue eyes” (Fig 1; a photograph taken in 1940). He added¹: “Her demonstrated motivation, industry, and keen interest in biology attracted the attention of faculty who encouraged and influenced her to continue on to the study of medicine.” She apparently took this advice, and was 1 of only 2 women in her class of 25 at Stanford School of Medicine.¹

After graduation in 1925 and an internship at San Francisco General Hospital, she worked half time for the Department of Public Health (in public schools and child welfare centers) and served Stanford as an assistant in pediatrics and medicine.¹ Her marriage rather quickly ended in divorce, but she retained the Loveless name. According to Dr.

Cohen, she “delighted in telling new acquaintances...that she was ‘loveless’ in name only.”¹

Years later, on a trip to London, she acquired a personal letter of introduction to Robert Cooke in New York and was offered a 3-week stay in his laboratory to begin to seek an explanation for why injections of pollen extract lowered a patient's hay fever symptoms during seasonal pollination.¹ This evolved into a 3-year, full-time fellowship. Loveless's work contributed to the identification of this allergy “blocking factor” as a pseudoglobulin (antibody) specific for the corresponding antigen, which could be produced even in nonallergic subjects by injections of pollen extract.³ Soon thereafter, Loveless discovered that this induced blocking antibody (unlike what then was called “skin sensitizing regain”) was thermostable.⁴

Loveless then moved into a full-time faculty position, as an instructor in medicine, at Cornell University Medical College—New York Hospital Medical Center, working in the allergy section.¹ Among her achievements was a study showing that blood transfused from patients with hay fever or hay asthma temporarily transferred the features of the illnesses to normal individuals, and that blood of nonatopic donors injected with ragweed pollen extracts (which contained blocking antibodies) resulted in sustained remission of symptoms and diminished skin test reactions in recipients who had suffered from asthma and hay fever.⁵

She subsequently took a leave from Cornell to train in immunohistochemistry with Michael Heidelberger at Columbia University—Presbyterian Hospital Medical Center.¹ This led to a list of papers on the properties of antigens, the nature of their antibodies, and serological studies using biophysical and immunochemical methods.¹ Notably, as recounted years later by Robert A. Good,^{6,7} she brought to Kimishige Ishizaka's attention, at a large meeting, her observation that countered his suggestion that reaginic antibodies occurred in the gammaA class, namely, the production of reagin in an otherwise healthy person with no detectable immunoglobulin A.⁸ According to Peery and Emrich,⁷ “Ishizaka graciously thanked Loveless and, with this new insight, returned to his research. Within 2 years, he had discovered, isolated, and purified immunoglobulin E and identified it as the reagin.”⁹

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Figure 1. Mary Hewitt Loveless, MD. Photograph by Bachrach, 1940.

However, Loveless is best known for her work on the prevention of insect-sting–induced anaphylaxis.^{1,2,7,10} Indeed, she was the first to report the benefit of using injections of small amounts of venom (instead of injections of extracts of the insect's entire body) to prevent, in most patients, insect sting–induced anaphylaxis (Fig 2 and 3).¹⁰ Sadly, her 1956 article¹⁰ (19 pages in length, but with only 2 figures) on the use of insect venom immunotherapy for the prevention of wasp-sting–induced anaphylaxis was virtually ignored for 18 years.

Why were her striking observations not more widely accepted? Those who have followed this field offer varying perspectives. In 1974, the work of Lichtenstein, Valentine, and Sobotka¹¹ confirmed, in their study of a single patient, Loveless's conclusion about the value of venom immunotherapy in this setting. In 1975, another study of a single subject provided additional support.¹² Finally, The Lichtenstein group published in 1978 a more extensive study, which included in-hospital sting challenges of placebo- or whole body extract–treated, as well as venom-treated, patients.¹³ The latter study definitively showed the value of venom treatment in largely suppressing skin and systemic reactions to active stings (only 1 of the 18 venom-treated patients who were actively stung developed mild urticaria).¹³ However, the tests of subjects not treated with venom were suspended before the entire groups could be challenged, because of the severity of 2 of the adverse reactions elicited by the test stings.¹³

As noted by Cohen,¹ when Loveless did her work, “a commercial source of venom to meet US Food and Drug Administration approval was not available; also, long-term controlled studies were required to establish safety and efficacy, especially over the use of *Hymenoptera* whole-body extracts, in which some instances of spontaneous loss of anaphylactic hypersensitivity might be attributable to the natural history of the disorder.” Another factor may have been her independence of thought (and opinion) and strong will—which seem, even today, to be less favored in women than in men. As noted by Valentine,² “skeptics might have outnumbered true believers” at “her infrequent public presentations in such a scientific forum as the Atlantic City ‘Federation’ meetings,” and her habit of using “well-worn, hand-typed (sometimes thumb-printed) lantern slides to help her data support her unorthodox

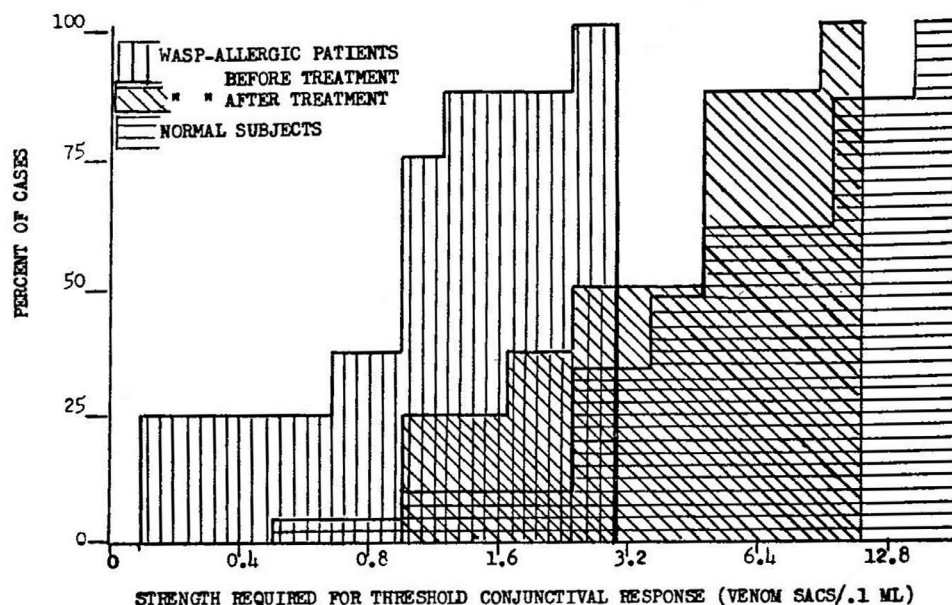


Figure 2. Figure 1 of Loveless MH, Fackler WR. Wasp venom allergy and immunity. *Ann Allergy*. 1956;14:347-366 (reproduced with permission of the journal).

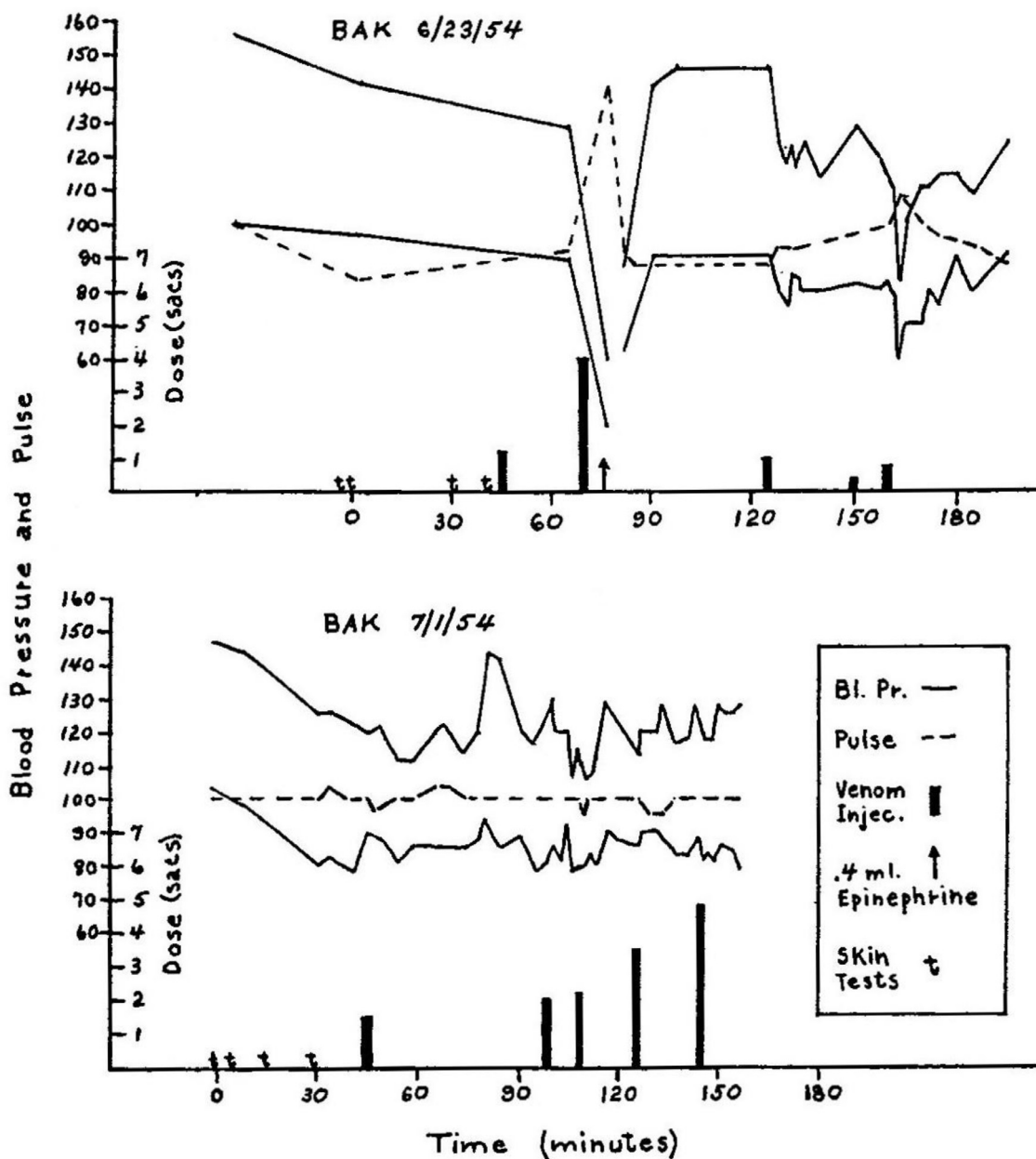


Figure 3. Figure 2 of Loveless MH, Fackler WR. Wasp venom allergy and immunity. *Ann Allergy*. 1956;14:347-366 (reproduced with permission of the journal).

argument for stings as treatment.” However, Valentine² also noted the “reasonableness of her discourse” and quoted Loveless’s description of how she obtained the venom: “Each autumn live wasps are procured either individually in the field with butterfly nets or preferably, in intact hives so that uniformity of species is assured.”¹⁰

As perusal of her 1956 paper shows,¹⁰ Loveless’s figures today appear rather “antiquated” in their style of data presentation (this paper contained the 2 figures reproduced herein [Fig 2 and 3], together with 6 tables). However, their importance in documenting her efforts to understand venom-induced anaphylaxis and its immunological treatment are nevertheless clear. Notably, she decided to refrain from subjecting patients with a history of anaphylaxis to insect stings to “deliberate sting tests” without prior courses of venom immunotherapy. In her own words:

“*Deliberate Sting Tests.*—In a number of instances patients consented to be stung, on the volar surface of the forearm, with the type of insect that had caused their severe reactions, and sometimes with

others as well. As during therapeutic courses, continuous observations were made throughout such experiments of the blood pressure, pulse, and local as well as systemic manifestations. To date, such tests have been attempted only after a course of immunization because of the risk of anaphylaxis in the untreated subject.”¹⁰

As she noted at the end of her paper:

“The use of the venom sac as the unit of measurement of wasp allergen is a temporary expedient, pending an arrangement for the speedy removal of sufficient venom to permit chemical assay on each batch. The adoption of a chemical standard should increase the reproducibility of the diagnostic tests and therapeutic results.”

“Carried out with specific antigen and with all precautions, the prophylactic management of wasp allergy is undoubtedly a life-saving measure to which the highly sensitized individual is entitled.”¹⁰

Valentine² noted that Anne Kagey-Sobotka (a junior author of the articles in 1974¹¹ and 1978,¹³ which confirmed and extended the scientific analysis of Loveless’s “venom immunotherapy”^{10,14})

appropriately acknowledged Loveless's important contribution in her thesis: "In 1977, Anne Kagey-Sobotka introduced her doctoral dissertation by writing: 'This thesis is dedicated to DR. MARY HEWITT LOVELESS, who, thirty years ago, first suggested the appropriateness of venom immuno-therapy, and who did pioneering work on the role of blocking antibody in allergic disorders.'"² This statement was very appropriately made then, and seems even more so today.

Although some of her scientific achievements took a long time to be fully appreciated, by the time of her death in 1991, Mary Hewitt Loveless was held in high regard by her peers. In its tribute recognizing her as a "pioneer clinical immunologist," the American Association of Immunologists noted that "Mary Loveless stood out among a very small group of Association members from whose work a rational understanding of asthma and human allergic disease would evolve."¹⁵ The American Academy of Allergy and Immunology wrote: "The legacy of her goals and achievements remains for all to respect, admire, and appreciate."¹⁵ The Division of Allergy and Immunology, Cornell University–New York Hospital Medical Center, noted, "For many years the allergy establishment did not accept her claim that insect venom was the only worthwhile immunizing agent in this treatment, but she argued her case well and was finally proved to be correct."¹⁵ And the American College of Allergy and Immunology added that it "takes a special measure of pride in noting that the publication of her seminal article on venom immunotherapy, which reversed the pattern of life-threatening reactions to stinging insects, was published in the society's journal, the *Annals of Allergy*."

As noted by Cohen,¹ "Mary Hewitt Loveless was known for treating patients in need regardless of their ability to pay." Her estate, according to Dr. Cohen, was built primarily on wise investments, not revenue derived from her practice. When she died, she left her more than \$4 million dollar estate to Stanford University School of Medicine to endow a fund "for the benefit of immunological research and study of life-threatening allergies."¹⁶ In this way, Mary Hewitt

Loveless's influence, and specifically her hope of helping those suffering from life-threatening allergies, continues.

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