

The ALLERGY ARCHIVES

Sheldon Cohen, MD, Editor

Pioneers and Milestones

Loveless on wasp venom allergy and immunity. Part 1

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*Books that told me
Everything about wasps,
Except why*

—Dylan Thomas¹

Had the Welsh poet Dylan Thomas (1914-1953) lived just 1 year longer, he would have had Mary Loveless' publication² to add a new element to his informational collection on wasps.

Mary Hewitt (1899-1991; Fig 1) was born in Clovis, California, of direct descent from prominent British families. Her parents had emigrated from England hoping to escape from the hardships of an economic depression only to find the need to cope with similar difficulties in the farmlands of Southern California.



FIG 1. Mary Hewitt Loveless (1899-1991).

^aMaterial for this biographic profile was, for the most part, taken and synthesized from personal communications (correspondence, discussions, and telephone conversations) between S. G. Cohen (the author) and Mary Loveless during her retirement years and from notes for the eulogy (delivered by the author) and tributes presented by other speakers at her memorial service held at the Saugatuck Congregational Church in Westport, Connecticut, June 22, 1991.

From the National Institute of Allergy and Infectious Diseases and the National Library of Medicine at the National Institutes of Health, Bethesda, Md.

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Reprint requests: Sheldon G. Cohen, MD, National Institute of Allergy and Infectious Diseases, 6610 Rockledge Blvd, Room 2012, MSC 6611, Chevy Chase, MD 20815.

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Lacking the financial support of family resources, Mary was nonetheless undeterred in pursuing educational goals. She worked in a variety of part-time jobs—waitress, clerk, secretary—through her college years at Stanford University (BA 1921), where she was remembered as bright, exquisitely attractive, tall, and slender, with striking blue eyes. 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. Following their guidance, she applied to Stanford's medical school and was admitted as only one of 2 young women in a class of 25.

After receiving an MD in 1925 and completing an internship at San Francisco General Hospital, she entered the private practice of general medicine in San Francisco, worked half time for the Department of Public Health in public schools and child welfare centers, and served as assistant in pediatrics and medicine at Stanford. Meanwhile, through marriage she acquired the name of Loveless, which she kept even after her divorce, and delighted in telling new acquaintances on introduction that she was "loveless" in name only.

After 10 years had gone by, Mary embarked on a transatlantic vacation voyage. What was intended only to be 6 months of holiday travel through Europe quite unexpectedly evolved into a change in the direction of her career. When visiting in London, by chance she met a physician to the royal family. Socially and professionally prominent, he knew Robert Cooke in New York and was familiar with ongoing pioneering work at the Roosevelt Hospital Asthma and Allergy Clinic. Pertinent to their conversation was the fact that during the previous 2 years, Mary held Stanford and University of California staff appointments to the allergy clinic at Children's Hospital and thus had been introduced to the developing field. Eagerly she accepted the proffer of a personal letter of introduction to Cooke and the suggestion that on her return to the United States, she arrange to visit with him in New York.

At their first meeting, Mary asked Cooke, "How do injections of pollen extract lower the patient's [hay fever] symptoms during [seasonal] pollination?" In response, Cooke invited her to spend the next 3 weeks in his laboratory to help in seeking an explanatory lead. What was intended to be a short-term, guest-worker stay turned into a 3-year, full-time fellowship; Mary never did return to practice in San Francisco.

Cooke and his associates in 1935 had discovered that the sera of patients with hay fever who received injection treatments with ragweed pollen extract had an inhibiting effect on the wheal and erythema skin test response to ragweed extract.³ Loveless' work on joining the group contributed to the identification of the blocking factor as a pseudoglobulin specific for corresponding antigen⁴ and that as an antibody it could be produced by injections of pollen extract,

even in nonallergic volunteers.^{5,b} Although fully occupied with obligations to patient care and laboratory projects, to which Cooke assigned first priority, Loveless had devoted what otherwise might have been free evenings and weekends to off-time hours in the laboratory pursuing special investigative interests. From that initiative, blocking antibody was identified.^c In 1937, Loveless also discovered the thermostable property of induced blocking antibody, a distinguishing identity that provided a method for its separation from naturally occurring skin sensitizing reagin, its isolation, and the study of its character.⁶

The following year, Loveless moved to the full-time faculty position of instructor in medicine at Cornell University Medical College—New York Hospital Medical Center to work in the allergy section under Horace Baldwin. In a prompt extension of her Roosevelt Hospital studies, she demonstrated that (1) blood transfused from patients with hay fever and hay asthma temporarily conferred all the attributes of the illnesses to normal recipients, and (2) blood transfused from nonatopic donors who were given injections of ragweed pollen extracts—and produced corresponding blocking antibodies—effected prompt and sustained remission of symptoms and diminished skin test reactions in recipient patients with hay fever and asthma.^{7,b} For the allergy clinic, she initially supervised testing procedures and, for several years, the preparation of test and treatment allergenic extracts. In a semi-independent mode of operation, she had her own laboratory and fellows and carried on a combination of private practice and clinical investigations primarily centered on immunologic studies of pollinosis and responses to injection treatments.

^bThese were pioneering studies carried out before the advent of critical evaluation and stringent requirements for approval by current-day institutional human subjects committees.

^cLoveless, complaining that her primary role in discovering the identity of blocking antibody was never acknowledged by Cooke, gave the following account. The concept for that study was hers alone, only to have it negated by Cooke as a “very poor idea.” Ordered not to conduct the investigation “for one minute” as a fellowship project, she did the requisite work on her own evening and weekend time. One year later, she had demonstrable data to show Cooke, but “he was too busy and put her report aside” until 4 months later, when she returned from a meeting of the American Academy of Allergy in Cleveland, encouraged by a discussion with the president-elect, Milton Cohen. On learning from Loveless that Cohen told her he had produced a ragweed-inactivating antibody in dogs, Cooke immediately had his chemist, Stull, determine whether the factor Loveless induced and identified was in the precipitable or nonprecipitable portion of the serum. He then promptly indicated he was “rushing (her finding) into print, so we get full priority.” When his secretary had the manuscript typed and ready for publication, a “disillusioned” Loveless learned that Cooke had taken first author’s credit.⁵ Loveless MH, personal communication to Cohen SG (the author), September 20, 1988.

In 1946, she took a period of leave from Cornell for training in immunochemistry with Michael Heidelberger at Columbia University—Presbyterian Hospital Medical Center. That broadening experience was reflected in her list of ensuing reports of properties of antigens, the character of their antibodies, and serologic investigations with biophysical and immunochemical methods. Loveless’ advancement was reflected in her escalating recognition as an accomplished scientist.

From her scientific colleague members of the American Association of Immunologists:

Mary Loveless was elected to membership in the American Association of Immunologists, a small, highly selective society of research biomedical scientists devoting individual and cooperative efforts to studying processes and nature of host defense. . . . In the advancement of this young field, Mary Loveless’ early contributions played a seminal role in immunology’s progress as a discipline developed from bacteriology, pathology, biochemistry and virology. . . . Mary Loveless stood out among a very small group of Association members from whose work rational understanding of asthma and human allergic diseases would evolve.⁸

A prolific and imaginative worker and multiply published author, she brought other interests and questions into her laboratory for clinical translation. Her studies represented a wide variety of interests that included human antibodies to insulin,⁹ food allergens that included the controversial issue of cottonseed allergen in cottonseed oil¹⁰ (a subject for which, at hearings on labeling held by the US Food and Drug Administration, she presented evidence for its absence), and disproving the initially purported identity of reaginic antibodies in the γ A serum fraction class through her study of an IgA-deficient allergic patient.¹¹ Less successful was her work designed to reduce the frequency of hyposensitizing injections to once a year by using allergenic pollen extracts and venom emulsified in mineral oil (designed to simulate Freund incomplete adjuvant used in experimental animal immunizations).¹² It was a technique that too frequently evoked the danger of rapid breakdown of emulsions with resultant systemic reactions or their retention with development of cysts and draining sinuses and thus was never approved by the US Food and Drug Administration.

In the mid-1950s, a new dimension was added to Loveless’ initiatives when she responded to the plight of a faculty colleague’s mother who had experienced 2 near-fatal anaphylactic reactions to bee stings, a nonpreventable and uncontrolled phenomenon recorded since antiquity, perhaps as early as the 26th century BC.¹³ Loveless had reason to believe that the then-conventional method of injection treatments with

whole-body extracts of insects had little if any value in immunizing systemically sensitive patients. At the time, the possibility of using Hymenoptera venom in immunotherapeutic procedures duplicating those with pollen extracts used for hay fever was not feasible. Other than a honeybee preparation used in the treatment of arthritis, a commercial source of venom was not available. Using a butterfly net, she then personally undertook the capture and collection of wasps, dissected and removed their venom sacs, and recovered and procured a supply of venom as a trial immunogen.

Apprehensive but not deterred, she worked with small trial series of patients over a 3-year period. Her design of protocols was based on individualized determination of starting doses derived from demonstration of threshold responses to dilutions of fractional contents of wasp, yellow jacket, honeybee, and hornet venom sacs; sequential injections of incrementally tolerated dosages in single day visits; periodic injections to maintain presumed immune and desensitized states; and calibration of total dosages in terms of numbers of source venom sacs. Reassured that her patients were protected against deliberate stings, she published the report of her results in 1956.^{14,d} She then moved on to immunization by deliberate stings (Fig 2), often with resultant reactions but under controlled conditions in which adrenalin and antihistamines could be promptly administered.

In 1958, Loveless moved to the National Jewish Hospital in Denver to establish a department of allergy



FIG 3. Mary H. Loveless, MD; 1959, as first Chief of the Allergy Department at the National Jewish Hospital, Denver.

and serve as its first chief (Fig 3). However, she remained for only a 1-year tenure, returned to Cornell Medical College–New York Hospital, and resumed her work and studies. When allergenic pollen extracts emulsified in mineral oil were introduced for treatment of seasonal hay fever with once yearly depot injections, she temporarily adapted the technique as a replacement for the annual sting.¹⁵

From a former Loveless trainee (T. M. Nall):

I was Dr. Mary Loveless' last research fellow at the New York Hospital, 1961 to 1963, dur-

^dLoveless explained that the second author, William Fackler, was a recent Cornell Medical College graduate who Loveless hired as a research assistant so that he might have a few months' income before entering practice. She tried to "convince him to become an allergist by staying on (with her) for a year or two. But he preferred to be a general country doctor in a small town somewhere, and even putting his name on [her] publication had no effect." Loveless MH, personal communication to Cohen SG, September 27, 1988.



FIG 2. Loveless placing a yellow jacket in position to deliver a sting. Wasp stings were found to be difficult to similarly induce unless the insect was incited by holding back its wings.

ing the period when she was trying to reduce the number of injections required for immunotherapy by using emulsion depot injections. Her records and follow-up on each injection, including proportions and shelf life, were meticulous. Depot emulsion therapy also was applied to insect venom but abandoned because venom quickly broke down the emulsion. We spent many hours each summer and fall dissecting out venom sacs and storing them in glycerin to be ready for extraction when they were needed for treatment in the late winter and early spring. It was a tedious task, but we had a jolly time. Dr. Loveless' scope of interests amazed me, ranging from insulin sensitivity to circulating blocking and neutralizing antibodies to double-blind, placebo-controlled food challenges to venom reactions and to streamlining treatment for ordinary hay fever. All this was investigated with a sense of adventure and pioneering. It was Dr. Loveless' enthusiasm for all these facets that convinced me to go into allergy.⁸

Yet the nature of the risks inherent in her studies was bound to generate controversy. Within the clinical community, she was criticized for what was considered to be cavalier conduct of investigation, particularly concerning the frequency of systemic reactions that treated patients experienced and the underreporting of their severity. Nonetheless, she held her ground. Ultimately, her rationale for championing the use of venom, rather than whole-body extract, as the immunogen of choice was confirmed when reports by other clinical investigative groups began to appear from 1974 through 1978.¹⁶⁻¹⁹

She continued to present reports of results of her studies and progress in advancing venom immunotherapy at national allergy conferences and society meetings, particularly in the standard format of short pre-



FIG 4. Loveless, in protective clothing, procuring live Hymenoptera by taking an intact hive to ensure uniformity of species in her colony.

sentations at the Federation of American Societies for Experimental Biology and published in periodic issues of *Federation Proceedings*. Concurrently, her work was featured in medical-themed magazines distributed to the profession (eg, *M.D.*, *Medical World News*, and *Modern Medicine*) and caught the public's eye in medicine and science sections of the popular lay media, such as *Life*²⁰ and *Newsweek*.²¹

In 1964, 5 years after returning from Denver, Loveless retired from her active faculty position at Cornell. By then she had risen in faculty rank to Associate Professor of Clinical Medicine and was credited with 63 publications.

From her academic colleagues in the Division of Allergy and Immunology at Cornell University–New York Hospital Medical Center: “[Mary Loveless] was an imaginative researcher, sometimes controversial, always stimulating. . . . [She] was a lively and provocative presence in our hospital setting for 26 years. . . .”⁸

It would be difficult, if not impossible, to separate the projected images of Mary Loveless' persona and Mary Loveless the medical scientist; her independence of opinion and strong will were so integrated with her projected feminine demeanor. Charm, pulchritude, and affectations were as evident in articulating presentations at the podium and speaking out at conferences as in her personal conversations. Passage of years made little if any difference. A special blend of beauty, intellect, and attraction persisted. In groups that gathered informally at national meetings, she was invariably among, and usually at the center of, seemingly enchanted, if not enamored, senior immunologists.

Loveless' academic retirement from Cornell Medical College–New York Hospital Center amounted to only a change in locale. Her interests in patient care and clinical investigations on pollen and insect sting allergies continued in her home office and lab-

oratory in Westport, Connecticut. She continued to write, bringing her publication list to 71, and served as consultant in allergy to the Sloan-Kettering Research Institute and Memorial Hospital in New York; the Norwalk, Connecticut, Hospital; and the US Food and Drug Administration.

The 18-year gap between Loveless' seminal contribution in 1956 and the earliest published reports in 1974 through 1976 that confirmed her imaginative initiative remained to be fully explained. From a reasonable viewpoint, there was the fact that 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 attributed to the natural history of the disorder. On the other hand, there were those who, knowing Mary Loveless, found some justification for her claim of bias in the lack of credit.

Beside criticism, mention of her work was often ignored at professional presentations and in literature reviews. Of the four journal case reports of efficacious diagnostic and therapeutic use of venom published from 1974 through 1976, one did not mention Loveless at all.¹⁷ The other 3^{16,18,19} only gave passing reference to her 1962 publication on repository therapy and periodic stings¹⁵ but did not cite the innovative studies she reported in 1956. Although her original work was subsequently cited by Reisman²² and Valentine²³ in the foremost text books of allergy and immunology published in 1978, as recently as 1986, not a single contributing author referenced her seminal contribution in the American Academy of Allergy, Committee on Insects' *Monograph on Insect Allergy*.²⁴

During her 25 postretirement years of undeterred industry, motivation, and personal and professional interests, Loveless continued to be visited by long-time patients. Seeking treatment, they were reassured by her vindication and her conviction that one controlled sting a year could both induce and maintain immunity against anaphylactic hypersensitivity to Hymenoptera venom.

Working in her laboratory was only part of the endeavor. She studied the nesting practices of wasps, hornets, yellow jackets, and honeybees. During favorable weather and seasonal environmental conditions, she carefully harvested and housed stinging insects in her garden (Fig 4), and for a readily available supply of wasps, she maintained them in natural habitat in the eaves of the attic of her home. After orchestrating their stings, she returned them to natural habitats to prosper and once again sting and immunize.

How ironic that in the process, at age 90, Loveless would be traumatized by an insect, a deer tick, the vector of Lyme disease. Ever the scientist, she was more intrigued by speculating on the “antigenicity of the high

molecular weight polysaccharide gum" secreted by the tick on attachment than the implications of her positive serology. On discussion of the possibility that antibiotic therapy might be indicated, her initial reaction was that she likely would not consider such a recommendation for several reasons: (1) her longstanding belief that treatment should never be based solely on the result of a laboratory test; (2) her past history of a distressing adverse reaction to tetracycline with symptoms that lasted 4 days; (3) deductions from her discovery of and work with blocking antibody that induced antibody was protective and not harmful; and (4) the clincher, her "full confidence in her immune system."^e

Mary Hewitt Loveless was known for treating patients in need regardless of ability to pay. Her estate was accumulated not from fees but from her lifetime avocation of paying close attention to her investments, daily devoting time to following the stock market and communicating with her broker. At her passing at age 91, the bulk of her more than \$4 million dollar estate was left to Stanford University Medical School to endow a fund "for the benefit of immunologic research and study of life-threatening allergies."²⁵

"Where bees are, there is [a] honey."^f

That was Mary Loveless.

Sheldon G. Cohen, MD
National Institute of Allergy and Infectious Diseases
National Library of Medicine
National Institutes of Health
Bethesda, Md

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^eLoveless MH. Personal communication to Cohen SG, September 27, 1988.

^fAdapted from an early 17th century proverb.