Creating a Buzz in the Field of Immunology:

Mary Hewitt Loveless and the Development of Venom Therapy for the Prevention of Sting-Induced Anaphylaxis

by Bryan Peery and John Emrich

Of the many images one might conjure of immunologists in the 1950s, one of the least likely might be that of a middle-aged woman, butterfly net in hand, chasing wasps in her garden. Yet, this is precisely how one eminent immunologist, Mary Hewitt Loveless (AAI '41), may have appeared on a typical summer day during that decade. An allergist and clinical immunologist, Loveless pioneered the use of venom, which she meticulously obtained from wasps and bees in her own backyard, to treat patients who were susceptible to anaphylaxis when stung by these insects of the order Hymenoptera. It is her work in developing and refining this allergy treatment, the first successful venom immunotherapy for patients with hypersensitivity to Hymenoptera stings, for which she is best remembered today.

Mary Hewitt Loveless's passport photo, 1955

Fiercely independent, Loveless was not afraid to engage in unconventional research methods. While her innovative approach to allergy treatment was largely ignored for much of her career, her persistence over more than one-half century of research ultimately won her accolades as the rest of the field embraced her methods.

Early Life

Mary Hewitt was born in Clovis, California, on April 28, 1899, to British immigrant parents who had fled an economic depression in England in the late nineteenth century. Settling in the southern California farming community in the 1890s, they found their economic conditions only moderately improved.[1] To attend college, Mary worked part-time as a waitress and secretary to pay her way through Stanford University, receiving a B.A. in biology in 1921. Encouraged by the faculty to pursue a degree in medicine, she entered medical school at Stanford as one of only two women in a class of 25 and earned her M.D. in 1925.[2] She married that same year and took the surname Loveless, the name she would use for the rest of her life, although the marriage soon ended in divorce.[3]

Following a medical internship year at San Francisco General Hospital, Loveless remained in the city to open a private practice. She also worked part-time for the California Department of Public Health and as an assistant in medicine at Stanford Medical School. It was while holding one of the Stanford staff appointments in the allergy clinic at Children's Hospital during the early 1930s that Loveless first became interested in allergy research.[4]

Loveless attributed her first opportunity to formalize her studies of allergy to a chance but fortuitous vacation encounter in 1935 with a London physician to the royal family.[5] It was not his access to Buckingham Palace that proved consequential for Loveless but rather his acquaintance with Robert A. Cooke (AAI '20), a renowned allergist at the Asthma and Allergy Clinic at Roosevelt Hospital in New York City. Given Loveless's interest and experience in allergy, the physician wrote a personal letter of introduction to Cooke for her and suggested that she stop in New York before returning to the Bay Area.[6]

1 In 1988–89, Sheldon G. Cohen (AAI '64) corresponded with Loveless and interviewed her over the telephone. This overview of Loveless's early life is drawn from the following two articles, which Cohen wrote based on his notes on those conversations: "In Conversation with Mary Hewitt Loveless, M.D.," *Allergy Proceedings* 10, no. 2 (1989): 153–55; "Loveless on Wasp Venom and Allergy Immunity. Part 1," *Journal of Allergy and Clinical Immunology* 112, no. 6 (2003): 1248–52.

2 Cohen, "In Conversation with Mary Hewitt Loveless, M.D.," 154; ibid., "Loveless on Wasp Venom and Allergy Immunity. Part 1," 1248.

3 Cohen, "Loveless on Wasp Venom and Allergy Immunity. Part 1," 1248.

4 Ibid.

5 Unfortunately, if Loveless named the physician with whom she met in her conversations with Cohen, he did not include it in his accounts. Cohen, "In Conversation with Mary Hewitt Loveless, M.D.," 154; ibid., "Loveless on Wasp Venom and Allergy Immunity. Part 1," 1248.

6 Ibid.

Loveless seized this opportunity to meet a pioneering researcher in allergy. She met with Cooke upon her return to the United States and was invited to stay as a guest researcher for three weeks to study the treatment of hay fever patients with injections of pollen extracts. Loveless must have impressed Cooke, for he offered her a research fellowship that kept her at Roosevelt Hospital for the next three years.[7]

Studies on Hay Fever and Blocking Antibodies

When Loveless arrived at Roosevelt Hospital in 1935, Cooke's laboratory was attempting to determine the mechanism by which ragweed pollen extracts offered protection to individuals who suffered from hay fever. Anecdotal evidence of the effectiveness of such treatment was readily available, as the practice had been used in clinics for nearly 20 years, but no one really understood how the treatment worked. By transfusing serum from treated patients to untreated patients, Cooke and his colleagues demonstrated that the immunity produced by pollen extract injections was transferrable, and they concluded that a blocking antibody specific to ragweed pollen must be responsible.[8] Loveless helped determine that this antibody was contained in the pseudoglobulin serum fraction[9] and demonstrated that even nonallergic patients produced it when injected with pollen extract.[10]

Department of Medicine, Cornell University Medical College, faculty and staff, 1946; Mary Hewitt Loveless is seated in back row, 4th from left

Medical Center Archives of NewYork-Presbyterian/Weill Cornell

Mary Hewitt Loveless with Michael Heidelberger, no date

Stanford Medical History Center

Loveless continued her studies of blocking antibodies and the use of pollen extracts in treating hay fever after her departure from the Cooke laboratory in 1938 for a joint appointment as an assistant physician at New York Hospital and instructor of medicine at Cornell University Medical College.[11] Here, Loveless published her "Immunological Studies of Pollinosis" as a series of five articles in *The Journal of Immunology* from 1940 to 1943.[12] In the first of these articles, she described the thermostable property of the blocking antibody, providing a method of separating the blocking antibody from the reagin using heat and allowing her to determine that the thermostable antibody exerted its neutralizing effect by binding antigen directly.[13]

7 Ibid.

8 Robert A. Cooke, James H. Barnard, Selian Hebald, and Arthur Stull, "Serologic Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever)," *Journal of Experimental Medicine* 62, no. 6 (1935): 733–50.

9 Arthur Stull, Mary Glidden, and Mary Loveless, "Protein Content of Human Serum," *Journal of Allergy* 7, no. 4 (1936): 333–36.

10 Robert A. Cooke, Mary Loveless, and Arthur Stull, "Studies on Immunity in a Type of Human Allergy (Hay Fever): Serologic Responses of Non-Sensitive Individuals to Pollen Injections," *Journal of Experimental Medicine* 66, no. 6 (1937): 689–96.

11 Cohen, "In Conversation with Mary Hewitt Loveless, M.D.," 155.

12 Mary Hewitt Loveless, "Immunological Studies of Pollinosis," *The Journal of Immunology* 38, no. 1 (1940): 25–50; ibid., 41, no. 1 (1941): 15–34; ibid., 44, no. 1 (1942): 1–8; ibid., 47, no. 2 (1943): 165–80; ibid., 47, no. 4 (1943): 283–92.

13 Mary Hewitt Loveless, "Immunological Studies of Pollinosis: I. The Presence of Two Antibodies Related to the Same Pollen-Antigen in the Serum of Treated Hay-Fever Patients," *The Journal of Immunology* 38, no. 1 (1940): 25–50.

To develop her skills in immunochemistry and further her understanding of blocking antibodies and their antigens, Loveless took advantage of a 1946 sabbatical to study under Michael Heidelberger (AAI '35, president 1946–47, 1948–49) at Columbia University College of Physicians and Surgeons.[14] Even as she developed advanced laboratory techniques, Loveless remained first and foremost a clinician committed to improving immunotherapy for the treatment of her allergy patients through clinical experimentation. At the 1946 AAI annual meeting in Atlantic City, she reported successfully applying the principles and techniques she had developed in treating hay fever to a patient who was allergic to insulin.[15] At times, her methods were highly controversial—perhaps none more so than when she injected patients with mineral oil emulsions, based on Jules Freund's (AAI '24, president 1955–56) adjuvant, in the hopes of maximizing the duration of immunity between boosters.[16]

The Turn to Insect Venom Allergies

In 1946, a colleague at Cornell asked Loveless if she knew of any treatment to prevent systemic allergic responses to insect stings. The colleague's mother had twice suffered near-fatal anaphylactic reactions to bee stings, and he thought Loveless's success in treating hay fever patients might enable her to help his mother.[17]

Stinger being extracted from hand

U.S. Department of Agriculture; Photo by Scott Bauer

Honey bee

Wikimedia Commons; Photo by Daniel Schwen

Hypersensitivity to Hymenoptera stings was known to be a relatively rare but severe condition. Physicians had reported hypersensitive patients experiencing a wide array of potentially fatal symptoms following stings, including a dramatic drop in blood pressure, coronary artery spasms, and swelling of the throat. Hypersensitivity to Hymenoptera venom was far less common than hypersensitivity to pollen, but, as one team of allergists noted, there was one crucial difference between the two: "In the former, inadequate protection may mean the difference between life and death; in the latter the difference is simply between comfort and discomfort."[18]

When Loveless began her studies on wasp-sting allergies, epinephrine was the primary means of preventing fatalities from anaphylactic shock. It had proved to be quite effective at combating anaphylactic reactions when administered immediately following a sting. But allergists were interested in preventing the onset of symptoms by desensitizing hypersensitive individuals. Beginning in 1939, clinicians reported success in desensitizing patients with whole-body extracts made by grinding up whole insects, leading many clinicians to conclude that "the sensitizing agent seems to be in the entire body of the insect."[19] Loveless began her experiments on Hymenoptera desensitization using whole-body extracts in 1948, but, after running chemical analysis on the whole-body extracts and pure venoms, she challenged what was then the conventional wisdom, arguing that the allergens were concentrated in the venom and hypothesizing that venom therapy would, for that reason, prove more effective than a regimen of whole-body extract injections.[20]

14 Cohen, "Loveless on Wasp Venom and Allergy Immunity. Part 1," 1249.

15 Mary Hewitt Loveless, "Coexistence of Two Antibodies for Crystalline Insulin in Human Serum," Abstracts of 1946 AAI Annual Meeting, *Federation Proceedings* 5, no. 1 (1946): 250.

16 Mary Hewitt Loveless, "Application of Immunologic Principles to the Management of Hay Fever, Including a Preliminary Report on the Use of Freund's Adjuvant," *American Journal of the Medical Sciences* 214, no. 5 (1947): 560–67; ibid., "Repository Immunization in Pollen Allergy," *The Journal of Immunology* 79, no. 1 (1957): 68–79.

17 Mary Hewitt Loveless, "The Sting: Prophylactic Venom Prevents Disaster," *Modern Medicine,* May 15, 1976, 54.

18 Harry L. Mueller and Lewis W. Hill, "Allergic Reactions to Bee and Wasp Stings," *New England Journal of Medicine* 249, no. 18 (1953): 729.

19 Robert L. Benson, "Diagnosis of Hypersensitiveness to the Bee and to the Mosquito: With Report on Successful Specific Treatment," *Archives of Internal Medicine* 64, no. 6 (1939): 1306–27; quote from Mueller and Hill, "Allergic Reactions to Bee and Wasp Stings," 727.

20 Mary Hewitt Loveless and William R. Fackler, "Wasp Venom Allergy and Immunity," *Annals of Allergy* 14, no. 5 (1956): 347–66. Fackler was a recent Cornell Medical College graduate who served as Loveless's research assistant. Loveless later explained that she included Fackler's name on the article to encourage him to enter the field of allergy research, but her generosity had little effect, as he "preferred to be a general country doctor in a small town somewhere." Loveless quoted in Cohen, "Loveless on Wasp Venom and Allergy Immunity. Part 1," 1250.

There was one tremendous obstacle to venom immunotherapy at the time: pure venom was not readily available. Undeterred, Loveless collected the insects herself, explaining in the methods section of her groundbreaking 1956 paper, "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."[21] She then anesthetized the insects and carefully removed their venom sacks, which she refrigerated for up to one year before grinding them up and injecting the venom into her patients. Although a tedious process, she grew quite proficient at it, reporting in 1964 that, after dissecting an estimated 30,000 insects over the years, she could "do a bug a minute."[22]


MEDICINE

Shots and bugs fight a rare but serious menace

August's Deadly Stings

Mary Hewitt Loveless as featured in "August's Deadly Stings," *Life*, August 9, 1963, p. 57

In 1953, Loveless began a small trial that involved injecting patients with progressively increasing doses of venom over the course of one or two days. Uncertainty regarding her patients' tolerance thresholds made this a dangerous procedure for her to undertake. Although Loveless noted that "in most instances" the treatment was accomplished "with only slight systematic reactions," she conceded, albeit rather euphemistically, that "in three patients, … the manifestations approximated (briefly) those described by the subject for his accidental stinging episode."[23] In other words, she had induced anaphylaxis in these subjects in her clinic. By 1956, she had determined a standardized schedule and reported that anaphylactic reactions "were entirely avoided."[24] Moreover, a series of live sting tests in her office, as well as accidental stings suffered by her patients outside of her clinic, suggested that her venom immunotherapy was effective.


Mary Hewitt Loveless, 1946

Medical Center Archives of NewYork-Presbyterian/ Weill Cornell

Even after she was named emeritus professor of medicine upon her retirement from Cornell University Medical College in 1964, Loveless continued refining her techniques, keeping wasps and bees in the garden of her Westport, Connecticut, home and treating allergy patients in her private practice, which she maintained for another 25 years. By 1976, she had treated over 300 patients with her venom immunotherapy and reported that six venom sacs injected over the course of a few hours could provide protection for up to one year.[25] Furthermore, she had begun replacing the annual booster shots of venom with live stings in her clinic for those of her patients who consented. Ten of her patients who lived in remote areas even "learned to net, chill, and apply the suitable species of wasp to the leg—with epinephrine and professional aid close at hand."[26]

The Loveless Legacy

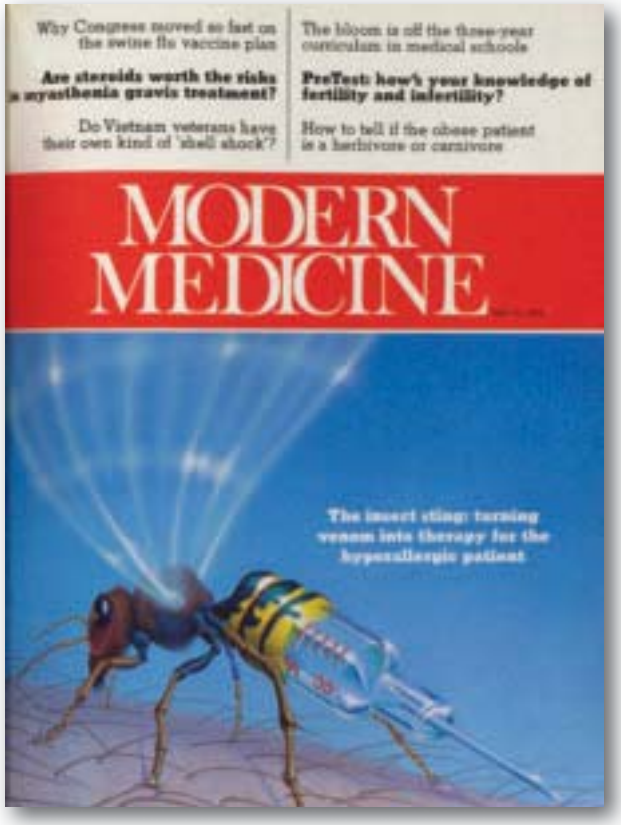
Loveless's "Wasp Venom Allergy and Immunity" was reprinted as the inaugural "landmark article" in *Allergy Proceedings* in 1989, but it was not welcomed as such when it was first published in 1956.[27] For the most part, scientists seemed to pay little attention at all, as whole-body extract remained the recommended treatment for Hymenoptera allergy. The popular press, however, was enamored with Loveless and her procedures. *Life* introduced Loveless's treatment regimen to a popular

21 Ibid., 347.
22 "August's Deadly Stings," *Life*, August 9, 1963, 58.
23 Loveless and Fackler, "Wasp Venom Allergy and Immunity," 355.
24 Ibid., 364.
25 Mary Hewitt Loveless, "The Sting: Prophylactic Venom Prevents Disaster," *Modern Medicine*, May 15, 1976, 54–57.
26 Ibid., 57.
27 Mary Hewitt Loveless and William R. Fackler, "Wasp Venom Allergy and Immunity (1956)," Landmark Article, *Allergy Proceedings* 10, no. 2 (1989): 157–60.

audience with the article "August's Deadly Stings" in 1963.[28] Fourteen years later, it was the colorful Loveless whom *Newsweek* profiled under the title, "Fighting Hives," although more recent entrants into the field of venom therapy were responsible for the acceptance of her technique among clinicians.[29]

The broader scientific community did not begin to embrace venom therapy until 1974, when, almost 20 years after Loveless first suggested using pure venom, Lawrence M. Lichtenstein (AAI '67), Martin D. Valentine (AAI '72), and Anne Kagey-Sobotka (AAI '78) of the Johns Hopkins University School of Medicine reported a single case in which they used honeybee venom to immunize a patient after whole-body extract failed to produce the desired effect.[30] Making only passing reference to Loveless's work, they noted, "Although some investigators have suggested treatment with the appropriate venoms, this treatment is not, in fact, possible within the constraints of federal regulations."[31] Even this reference was not to Loveless's 1956 article but rather to a follow-up study that she reported in *The Journal of Immunology* in 1962.[32]

The group at Hopkins published the results of a single-blind controlled trial on venom therapy in 1978.[33] They divided 60 patients into three groups, treating the first with venom, the second with whole-body extract, and the third with a placebo. Of the 18 patients treated with venom who agreed to a sting test, only one had mild systemic reactions. Members of the whole-body and placebo groups, on the other hand, fared so poorly that the trials were terminated early. Seven of the 11 of those treated with whole-body extract suffered severe systemic reactions following the sting test, as did seven of the 12 who received a placebo. Whole-body extract, the treatment method that had been favored by allergists since 1939, proved no more effective than the placebo. The following year, in 1979, the U.S. Food and Drug Administration finally approved venom-sac extracts for use in the therapeutic treatment of patients with Hymenoptera venom allergies.[34]



Cover of the May 15, 1976, issue of *Modern Medicine*, featuring Mary Hewitt Loveless's article, "The Sting: Prophylactic Venom Prevents Disaster"

Anterior view of a bald-faced hornet, *Dolichovespula maculata*

Centers for Disease Control and Prevention; Photo by Dr. Gary Alpert, Harvard University

28 "August's Deadly Stings," *Life*, August 9, 1963, 57–60.

29 Matt Clark with Dan Shapiro, "Fighting Hives," *Newsweek*, April 11, 1977, 65–66.

30 Lawrence M. Lichtenstein, Martin D. Valentine, and Anne K. Sobotka, "A Case for Venom Treatment in Anaphylactic Sensitivity to Hymenoptera Sting," *New England Journal of Medicine* 290, no. 2 (1974): 1223–27.

31 Ibid., 1224.

32 Ibid., 1227; Mary Hewitt Loveless, "Immunization in Wasp-Sting Allergy through Venom-Repositories and Periodic Insect Stings," *The Journal of Immunology* 89, no. 2 (1962): 204–15.

33 Kevin J. Hunt, Martin D. Valentine, Anne K. Sobotka, Allen W. Benton, Frank J. Amodio, and Lawrence M. Lichtenstein, "A Controlled Trial of Immunotherapy in Insect Hypersensitivity," *New England Journal of Medicine* 299, no. 4 (1978): 157–61.

34 Martin D. Valentine, "Loveless on Wasp Venom and Allergy Immunity. Part 2," *Journal of Allergy and Clinical Immunology* 112, no. 6 (2003): 1254.

Members of the Hopkins group later acknowledged, to varying degrees, Mary Hewitt Loveless's role in pioneering venom therapy. In 1977, Kagey-Sobotka, the most junior member of the research team, dedicated her dissertation to Loveless, "who, thirty years ago, first suggested the appropriateness of venom immunotherapy."[35] Valenine later contributed an article on the significance of Loveless's research to "The Allergy Archives" series in the *Journal of Allergy and Clinical Immunology.*[36] Lichtenstein, however, remained somewhat skeptical, pointing out that Loveless "never carried out controlled studies" and questioning "whether her once- or twice-a-year sting regimen was really effective."[37]

The same fierce independence and penchant for the unconventional that drew criticism also won Loveless many admirers. Robert A. Good (AAI '57, president 1975–76), in his AAI President's Address, recounted one instance in which Loveless's boldness contributed, at least indirectly, to a major discovery in basic immunology. Speaking in front of a large audience at the Fifth International Congress of Allergology and Clinical Immunology in Madrid in 1964, Kimishige Ishizaka (AAI '58, president 1984–85) presented experimental results that demonstrated that IgA-rich fractions contained reagins and suggested that IgA might be the reaginic immunoglobulin. Good recalled that Ishizaka's talk "convinced me and, I think, almost everyone present," but Loveless rose to challenge Ishizaka's hypothesis. She reported having a patient who produced reagins, though he lacked IgA entirely. Ishizaka graciously thanked Loveless and, with this new insight, returned to his research. Within two years, he had discovered, isolated, and purified IgE and identified it as the reagin.[38]

It may have taken decades for some of her scientific achievements to be fully appreciated, but by the time of her death in 1991, Mary Hewitt Loveless was held in high regard by her peers. The AAI tribute to Loveless noted that she "stood out among a very small group of Association members from whose work a rational understanding of asthma and human allergic disease would evolve," and recognized her as a "pioneer clinical immunologist."[39]

Honey bees on honeycomb

U.S. Department of Agriculture; Photo by Scott Bauer

Even after her death, Loveless contributed to the field of immunology. An avid investor who amassed a sizable estate by carefully following the stock market on a daily basis, she bequeathed nearly $4 million to her alma mater, Stanford University School of Medicine, "for the benefit of immunologic research and study of life-threatening allergies."[40] Stanford, in turn, established an endowed chair in her honor, the Mary Hewitt Loveless, M.D., Professorship in the School of Medicine, a title held by Stephen J. Galli (AAI '80) since it was first awarded in 1999. ■

Bryan D. Peery, Ph.D., AAI Assistant Historian

John S. Emrich, Ph.D., AAI Historian

35 Quoted in ibid., 1252.

36 Ibid., 1252–54.

37 Lawrence M. Lichtenstein, "Reply," Correspondence, *Journal of Allergy and Clinical Immunology* 96, no. 6 (1995): 1019.

38 Robert A. Good, "Runestones in Immunology: Inscriptions to Journeys of Discovery and Analysis," *The Journal of Immunology* 117, no. 5 (1976): 1416; Kimishige Ishizaka, Teruko Ishizaka, and Margaret M. Hornbrook, "Physicochemical Properties of Reaginic Antibody, IV. Presence of a Unique Immunoglobulin as a Carrier of Reaginic Activity," *The Journal of Immunology* 97, no. 1 (1966): 75–85; ibid., "V. Correlation of Reaginic Activity with E-Globulin Antibody," *The Journal of Immunology* 97, no. 4 (1966): 840–53.

39 Reprinted in "In Memoriam: Mary Hewitt Loveless, M.D., (1899–1991)," *Allergy Proceedings* 12, no. 5 (1991): 359.

40 Cohen, "Loveless on Wasp Venom Allergy and Immunity. Part 1," 1252.