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Celebrating the History of The American Association of Immunologists (AAI)

Founded in 1913, AAI celebrated its centennial in 2013. To mark this milestone, AAI began a number of initiatives to preserve and promote the proud legacy of the association and its members. AAI staff historians and scientists continue rigorously researching and archiving materials to feature the most significant advances in immunology from the past 111 years—and the many AAI members responsible for them.

The history of AAI is preserved and presented through:

- commemorative articles published in the AAI Newsletter
- interviews conducted as part of the ongoing AAI Oral History Project
- first-person stories recorded in the AAI StoryBooth at AAI annual meetings
- profiles of past AAI members including AAI presidents, editors-in-chief of *The Journal of Immunology*, and the many Nobel laureates and Lasker recipients in the rich AAI heritage
- the AAI Centennial Timeline, a 120-foot-long display featured at seven AAI annual meetings since its debut in 2013, chronicles the advances in science and immunology made through 2023 by AAI members and other scientists, placing those developments alongside key political and cultural events in U.S. and world history
- a digital version of the AAI Timeline, which includes citations and references (www.aai.org/timeline)
- history exhibits at AAI annual meetings, featuring the AAI members, institutions, and diseases shaping immunology research in the region

These articles, oral history interviews, profiles, and more are posted in the history section of the AAI website at www.aai.org/about/history. Here, we present the articles published in the AAI Newsletter between December 2011 and March 2024.

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The Founding of AAI

Medical College, University of Minnesota (c.1908)

Image: Library of Congress, Prints & Photographs Division, Detroit Publishing Company Collection



Early moving assembly line at Ford (ca.1913)
Library of Congress, Prints & Photographs Division

As the Centennial year of The American Association of Immunologists (AAI) approaches, we can look back and appreciate the incredible advances that were taking place in the United States and the world in 1913.

- ▶ The Ford Motor Company introduced the first moving assembly line
- ▶ The United States dedicated its first transcontinental road – the Lincoln Highway – linking New York and California.
- ▶ Construction on the Panama Canal, one of the seven wonders of the modern world, was finally completed.
- ▶ Congress created the Federal Reserve System to establish stability in the banking system.
- ▶ Woodrow Wilson was sworn in, becoming the first and only U.S. president with a Ph.D.¹
- ▶ The Progressive Era ideal that efficiency, expertise, an professionalism could overcome societal problems and, potentially, nature itself was beginning to infuse federal government programs and public discourse.
- ▶ New technology and enhanced training were dramatically increasing the rate of discovery and, with it, specialization in science and medicine—as evidenced by the many *New York Times* front-page stories about new treatments and the causes of diphtheria, rabies, cancer, and tuberculosis.

1. Woodrow Wilson earned his doctorate in history and political science in 1886 from Johns Hopkins University.

On the unusually warm evening of June 19, 1913, far from the national spotlight or any mention on the front pages of newspapers, a small group of physicians met on the campus of the University of Minnesota to form a society for a new medical specialty. This new society would help define immunology as bona fide area of specialization and would eventually become the preeminent professional association for immunologists in the world.



Martin J. Synnott

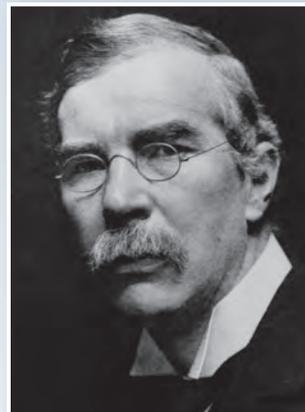
Image provided by The American Association of Immunologists Collection, Center for Biological Sciences Archives, University of Maryland, Baltimore County

These physicians had been attending the annual meeting of the American Medical Association² and were meeting at the invitation of Martin J. Synnott, a private practice physician from Montclair, New Jersey, who had made previous, failed attempts to organize a society of North American disciples of Sir Almroth Wright³.

On this day, however, he was finally successful, and The American Association of Immunologists (AAI) was founded. The new society quickly

organized around a definitive name, a set of objectives, and leadership that would build the foundation for lasting success. In just a few years, the new society would lead in legitimizing a new scientific discipline as the group established its own annual meeting and created what was to become the most highly acclaimed peer-reviewed scientific journal in its field *The Journal of Immunology (The JI)*.

The idea to form a new professional organization had first occurred to Synnott (AAI 1913, secretary 1913–1918) in early 1912. As a former student of Sir Almroth Wright (AAI Honorary 1914), Synnott wanted to bring together the men⁴ in the United States and Canada who had trained with Wright and shared his vision of the emerging promise of vaccine therapy. In 1912, Synnott wrote to 49 former students of Wright's and received 40 favorable responses to his proposal for forming "The Society of Vaccine Therapists." These 40 physicians were in practice located across the continent, isolated from other colleagues schooled in Wright's premise that "the physician of the future would be a vaccine therapist."⁵ Wright's "disciples" were not sufficiently organized in any fashion to promote awareness of the promise held by vaccine therapies.



Sir Almroth Wright

Image provided by The American Association of Immunologists Collection, Center for Biological Sciences Archives, UMBC

Wright was the founder and director of the Inoculation Department at St. Mary's Hospital in London and the Praed Street Laboratories. His laboratories were focused on the concept that "recovery from all infective diseases must be largely determined by the development of 'antibodies' in the patient's blood and that this process could be probably stimulated by inoculation of the appropriate vaccine." Wright advocated for more than mere vaccination, promoting

a technique of vaccine therapy that he had developed. The therapy was based upon the premise that a sick patient could be injected with appropriate levels of a vaccine to "exploit the uninfected tissue in favor of the infected." His initial success in the early 1900s with an effective anti-typhoid inoculation technique had made the Praed Street Laboratories a magnet for new students. This inoculation technique was adopted by the British War Department in 1914 as standard procedure. Its success had earlier led to Wright's being inducted into knighthood.⁶

Despite the British military's adoption of his inoculation technique and his 1906 induction into knighthood, Wright's vaccine therapy research in 1912 was not appreciated or widely employed outside of England. Synnott's efforts to form the new Society of Vaccine Therapists were intended to promote awareness of the field's promise. Despite the 40 positive responses Synnott had received for the concept of the new society in 1912, too few of his colleagues were available for

2. The exact number of attendees at the organizing meeting of AAI is unknown
3. For more information on Almroth Wright see: Michael S. Dunnill, *The Plato of Praed Street: The Life And Times of Almroth Wright* (Royal Society of Medicine: London, 2001); Zachary Cope, *Almroth Wright: Founder of Modern Vaccine-therapy* (Nelson: London, 1966); Leonard Colebrook, *Almroth Wright: Provocative Doctor and Thinker* (William Heineman: London, 1954).
4. Almroth Wright was a publicly acclaimed anti-suffragist, and he never allowed women into his laboratory. There were no women scientists under his tutelage to invite to join
5. Almroth E. Wright, *Studies on Immunisation and Their Application to the Diagnosis and Treatment of Bacterial Infections* (Archibald Constable & Co.: London, 1909).
6. Leonard Colebrook, "Almroth Edward Wright. 1861-1947," *Obituary Notices of Fellows of the Royal Society*, 6, no. 17 (1948): 299-300. The adoption of Wright's anti-typhoid inoculation technique made England the only country to have troops resistant to typhoid at the onset of the First World War. Wright was knighted in 1906 for recognition of his research and successes in preventive inoculation against the enteric group of infections, notably typhoid fever.

the proposed organizational meeting. He soon made another attempt, calling for a meeting on the evening of May 5, 1913, at the Hotel Raleigh, Washington, DC, during the annual meeting of the Association of American Physicians. Still, there were too few participants. Undeterred, Synnott scheduled the successful Minneapolis organizational meeting from which the new professional society emerged that summer.

In Synnott's view, it was a society of vaccine therapists. The scope and membership of the new society formed at the meeting, however, departed significantly from Synnott's initial concept, encompassing a broader view of the science and clinical practice. This difference was reflected in the name the new society: The American Association of Immunologists

The name is attributed to Gerald B. Webb, a nationally renowned tuberculosis physician and researcher who would become the first president of the society. Although he had trained with Wright and was a devoted disciple, he was concerned that Synnott's proposed Society of Vaccine Therapists would impose restrictions on future growth of the new organization.⁷ For Webb, linking a society exclusively with vaccine therapy posed two major problems. First, he was aware that Wright's theories and methods were viewed with skepticism in England and Europe, and he sought to avoid this tarnish.⁸ Second, restricting a society to a single process would limit its interest. If the new society was perceived as anchored only in vaccine therapy, Webb feared it would not attract clinicians and researchers in other related, growing fields, such as experimental pathology. To make the society more inclusive and flexible, the founders expanded the list of eligible members to include physicians and researchers who had trained with Élie Metchnikoff⁹ Paul Ehrlich, August von Wassermann, as well as in "other famous laboratories in Europe."¹⁰ They also sought a name for the organization that would connote a broader mission and position the society for growth with scientific and medical advances. They settle upon using a new term, "immunology," in the name.

According to the *Oxford English Dictionary*, the word "immunology" had entered the English language through its use by two future AAI members and presidents shortly before the founding of AAI. In 1909 Ludvig Hektoen (AAI president 1926) was the first to use the word. He did so in his article, "Opsonins and Other Antibodies," in *Science*.¹¹ Hektoen used the term only once – and only in passing – when referring to the law of opsonin production: "In the language of immunology any substance capable of giving rise to antibodies in suitable animals is called an antigen." Then, a mere three months before AAI was formed, Frederick P. Gay (AAI 1918, president 1921) defined immunology as a distinct scientific discipline in the *Journal of the American Medical Association*. In his article, "Immunology: A Medical Science Developed



Gerald B. Webb

Image provided by The American Association of Immunologists Collection, Center for Biological Sciences Archives, UMBC

through Animal Experimentation," Gay asserted that "[t]he science of immunity, or immunology, would explain the mechanism by which the animal body is enabled to resist disease."¹²

In 1913, Webb was well aware of Wright's 1909 proclamation that "the physician of the future will be an immunisator," and, as his biographer makes clear, Webb preferred Gay's broad definition of "immunology" to the narrow denotation of Wright's "immunisator," referring very specifically to an immunizer, inoculator, or vaccine therapist¹³

Nearly 65 years later, the wisdom of Webb's preference was praised for its importance to the recognition of immunology as a scientific discipline when David Talmage (AAI 1954, president 1978–1979) stated, "I believe we can properly attribute [immunology's] prominence in our vocabulary, if not its invention, to Dr. Webb."¹⁴

Beyond naming the new society at the founding meeting, the members also created a mission statement in the form of three objectives. The first two reflected the inclusiveness set forth with the use of "immunology" in the name. "To unite the physicians of the United States and Canada who are engaged in the scientific study of immunology and bacterial therapy. To study the problems of immunology, and to promote by its concerted efforts scientific research in this department." The third objective clearly stemmed from Synnott's intention to promote awareness of Wright's teachings: "To spread a correct knowledge of vaccine therapy and immunology among general practitioners." The dues of the association, to be fixed annually by the Council, were "not to exceed Five Dollars (\$5.00)."¹⁵

7. Helen Clapesattle, *Dr. Webb of Colorado Springs* (Colorado Associated University Press: Boulder, CO, 1984), 215.

8. Clapesattle, 215.

9. Born Ilya Ilyich Mechnikov, he was also known as Élie Metchnikoff

10. Martin Synnott, "A Historical Sketch," (1914). AAI Archives. It is unknown which laboratories Synnott and Webb considered "famous."

11. "Immunology," *Oxford English Dictionary*, <http://www.oed.com> (accessed 19 March 2012); Ludvig Hektoen, "Opsonins and Other Antibodies," *Science*, 29, no. 737 (1909): 241–248. It is unclear when Dr. Hektoen was elected a member of AAI. It is possible it was 1919, as the election information from that year is missing in the AAI Archives.

12. *Oxford English Dictionary*; Frederick P. Gay, "Immunology: A Medical Science Developed through Animal Experimentation," *Journal of the American Medical Association*, 56, no. 8 (1911): 578–583.

13. Clapesattle, 216.

14. David W. Talmage, "Presidential Address: Beyond Cellular Immunology," *The Journal of Immunology* 123, no. 1 (1979): 1.

15. Minutes of the First Annual Meeting of The American Association of Immunologists, 22 June 1914. AAI Archives.

Requirements for election to the membership were established. A candidate had to be nominated by one member, be endorsed by two additional members, have provided the AAI secretary with “papers” that indicated the character of his or her contributions to immunology, and have “at least one published contribution to the science of immunology.” The candidate had to be a “graduate of medicine,” although no specific degree requirements were mentioned

The officers elected during the 1913 meeting were We (president), Synnott (secretary), George W. Ross (vice-president), Willard J. Stone (treasurer), , and five councillors, including A. Parker Hitchens (chairman of the council), Oscar Berghausen, Campbell Laidlaw, Henry L. Ulrich, and J.E. Robinson. The officers set a date and location for their ne meeting, the first AAI annual meeting: June 1, 1914, in Atlantic City, New Jersey.¹⁶

Although the date was eventually moved to later in the month, 18 of 52 initial AAI members did, in fact, convene for the first annual meeting of the society on June 22, 1914, at the Hotel Chelsea in Atlantic City. According to the minutes of the first annual meeting, “the work of developing the society had progressed slowly but effectively” since Minneapolis ¹⁷ Membership in AAI had increased from its 52 initial members to 59 with the election of seven new scientists at the meeting. The leadership was kept in place as ll of the officers wer re-elected, and a draft of the constitution and by-laws was proposed to provide organizational stability. The impetus for future growth, however, was provided by the interesting science presented at this first annual meeting and the founders’ creativity in plans for membership development.

Attendees at this meeting discussed a range of diverse topics during the one-day conference. Presented at the meeting were a few papers on techniques or hypotheses that would not be borne out by later experimentation and that would not be considered “immunology” by today’s standards, but several of the speakers presented studies and technical innovations that did presage the ultimate focus of the field (See *Science at the First AAI Annual Meeting*, p. 7.)

The members at this first meeting may have had littl experience in membership development, but they did not lack imagination for novel ways to enhance the prestige of membership in the society. They established two discretionary membership classes defined vaguely enough to convey member status on a group of prestigious British physicians focused on vaccine therapy at St. Mary’s Hospital.¹⁸ The first of these special membership classes created was the Honorary Member category, to which they elected Almroth Wright and Captain S. R. Douglas.¹⁹ The second category was that of Corresponding Member, to which they elected Alexander Fleming and John Freeman.²⁰

Of the 59 Charter Members, the majority were clinicians or professors, and, in keeping with the trend prior to the Second World War, there were very few, if any, Ph.D.s.;²¹ most, if not all of the Charter Members, were M.D.s. The association had a broad geographical reach and included members from as far north as Toronto, Canada, and as far south as Temple, Texas; from as far east as Boston, Massachusetts, and as far west as Honolulu, Hawaii. The Philadelphia region boasted the most early members (12), followed by New York City region (11), and Ohio (7). The Charter Members also included a constituency that would have been anathema to the vehemently anti-suffrage Wright: two women ²²

Growth of the new society was robust enough that, by the time of that first annual meeting in Atlantic City, even Synnott seems to have accepted the utility of Webb’s preferred term of “immunologist” over “immunisator.” When asked to offer attendees an account of the founding of the society, Synnott took liberties in paraphrasing Wright’s famous assertion, stating that “the physician of the future would be an *immunologist*,” and that the new society “would in a few years be one of the most important medical organizations on this continent.”²³ Though Webb is often cast as the most important founding member, two less heralded Charter Members were equally important to the continued success of the new society: A. Parker Hitchens (AAI 1913, Council president 1913–1917) and Richard Weil (AAI 1914, president 1916–1917). As the president of the Council, Hitchens drafted the first AAI Constitution and By-laws, which established how the organization was to be governed. He was also almost solely responsible for making sure that AAI was a co-founder of *The Journal of Immunology* with the New York Society for Serology and Hematology (see *AAI Newsletter*, Dec. 2011).

Weil had an equal, if less obvious, impact on the association during his abbreviated membership. He was a Charter Member

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16. “Medical News,” *Journal of the American Medical Association* 61, no. 23 (1913): 2079.
 17. Minutes of the First Annual Meeting of The American Association of Immunologists, 22 June 1914. AAI Archives.
 18. When the AAI Constitution and By-Laws document was adopted in April 1917, the only membership category was “Active.” Honorary and Corresponding memberships were eliminated. The majority of the Honorary Members were transferred to Active membership and the Corresponding Members were all removed from the AAI membership rolls. The Honorary membership returned in 1935 but was then very similar to the current AAI Emeritus Member classification
 19. S. R. Douglas, F.R.S. (1871–1936) was a bacteriologist and captain in the R.A.M.C. In 1902, Douglas became an assistant to Wright, was the initial assistant director of the inoculation department at St. Mary’s Hospital, and in 1914, became the deputy director of the National Institute for Medical Research (UK). In 1903, Wright and Douglas published a paper on the role of the body fluids in phagocytosis, which helped stimulate work on vaccines and vaccine therapy.
 20. Alexander Fleming (1881–1955), a student and protégé of Wright’s, is best known for his discovery of penicillin in 1928 for which he was awarded the Nobel Prize in Physiology or Medicine in 1945. John Freeman, D.M. (1877–1962) was one of Wright’s first disciples, who spent his entire professional career at St. Mary’s Hospital. Primarily a bacteriologist, Freeman also carried out research in allergy and asthma.
 21. The founders classified those who joined AAI before 1915 as Charter Member
 22. “Roll of Charter Members,” c. 1914. AAI Archives.
 23. Martin Synnott, “A Historical Sketch,” c.1914. AAI Archives. [emphasis added]

and served as AAI president from 1916 to 1917, but his most enduring contributions to the society were in his recruitment of members and his early assistance to *The JI*. Shortly before his retirement, Arthur Coca (AAI 1916, secretary-treasurer 1918–1945, editor-in-chief 1920–1948) singled out Weil, praising him for having “used his considerable influence to induce outstanding immunologists to join [AAI].”²⁴ Coca also recalled Weil’s “more optimistic” view of the new journal, which led him to contribute four papers for the first issue. Weil’s papers, in Coca’s estimation, “helped materially” to start the journal.²⁵



Richard Weil

Image provided by The American Association of Immunologists Collection, Center for Biological Sciences Archives, UMBC

Further, Coca credited Weil for his role in selecting the initial editorial board for *The JI*. The founders of AAI were enjoying great momentum, but all of their good efforts were soon to be abruptly interrupted.

On April 6, 1917, while AAI members were in New York City for their fourth annual meeting, they learned that the United States Congress had declared war on Germany. The “war to end all wars,” which had been raging in Europe for almost three years, had now become a reality for America,

and her citizens quickly mobilized for war. As in all other areas of American life, the war had an immediate and lasting impact on the nascent society.

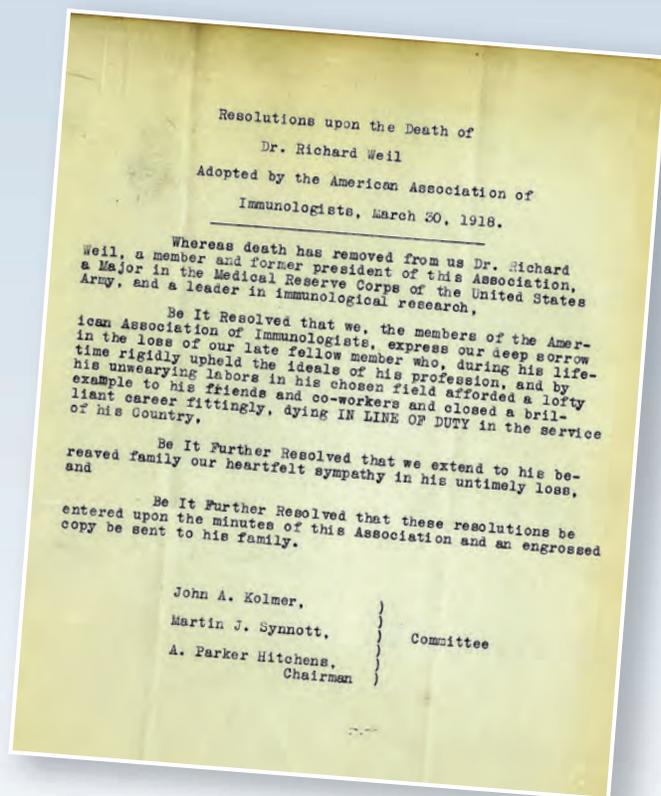
On the same day that they learned the United States had entered the First World War, members of the AAI Council passed the following resolution of shared sacrifice

Whereas the Government of the United States may soon need the services of trained bacteriologists and immunologists and the facilities of their respective laboratories,

Be it Resolved, that the American Association of Immunologists in meeting on April 6th and 7th, 1917, as a body and as individuals, offer their services and the facilities of their laboratories to the Federal and respective State governments; and,

Be it further Resolved, that the secretary of the American Association of Immunologists send a copy of this resolution to the Secretary of War.

Many members of AAI and others in the medical and scientific community quickly joined the war effort. AAI President Weil



Weil Resolution

Image provided by AAI

was among them. A number of members stayed in their laboratories to carry out wartime research, while others enlisted in the U.S. Army Medical Reserve Corps and were sent to bases around the country.

The focus of the laboratories in wartime shifted to meet the needs of the military, conducting research into the pandemic influenza²⁶ trench diseases, and wound-related infections. Wartime mobilization also directly affected the society’s leadership. Willard Stone had to relinquish his duties as AAI treasurer when he was stationed at the base hospital at Fort Riley, Kansas, in 1917.²⁷ And Weil was assigned first to Fort Benjamin Harrison near Lawrence, Indiana, and then to Camp Wheeler, outside of Macon, Georgia, as chief of medical service to help quell an outbreak of measles and pneumonia at the camp. Tragically, Weil died of complications from pneumonia on November 19, 1917, only a few months after arriving at the camp.²⁸ He was the only AAI member to die during the war, but

24. Letter from Arthur F. Coca to Geoffrey Edsall, 30 August 1915. AAI Archives

25. Arthur F. Coca, “AFC History beginning of Journal of Immunology,” undated [c. 1951]. AAI Archives.

26. For more detail on the pandemic influenza research during the First World War, see John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (Penguin Books: New York, 2005); Alfred W. Crosby, *America’s Forgotten Pandemic: The Influenza of 1918*, 2nd ed. (Cambridge University Press: New York, 2003); Dorothy A. Pettit and Janice Bailie, *A Cruel Wind: Pandemic Flu in America, 1918–1920* (Timberlane Books: Murfreesboro, TN, 2008).

27. Letter from Willard J. Stone to John A. Kolmer, 24 December 1917. AAI Archives. Fort Riley has been identified by some historians as Ground Zero for the pandemic influenza

28. *The New York Times*, “Major R. Weil Dies at Camp Wheeler,” 20 November 1917. See also; “Major Richard Weil, M.O.R.C.,” *The Journal of Immunology* 3, no. 1 (1918): IN1–vii.

his death dealt AAI a profound loss. At its fifth annual meeting in 1918, AAI passed a resolution honoring his legacy.²⁹

The year 1920 marked another important year in the history of AAI. It was in that year that the New York Society for Serology and Hematology (SSH) and AAI were merged. SSH had “omitted its monthly meeting for over a year and, since the function of the societies had been in a measure superseded by the American Association of Immunologists, it was deemed advisable to consolidate the societies.”³⁰ Its members were provided the option of AAI membership. This event added significantly to the size of the organization by adding a number of SSH members to the AAI rolls.³¹ The absorption of SSH by AAI eliminated the only other organization in the United States “having interest in immunological matters.”³² Additionally, *The JI* became the “property and official organ” of AA.³³

By the close of 1920, AAI boasted a membership of 152 physicians and scientists from 22 states, the District of Columbia, and Canada, including 16 women members.³⁴ The membership included the preeminent American scientists and physicians Simon Flexner, Theobald Smith, Oswald Avery, Hans Zinsser, Rufus Cole, Victor Vaughn, William H. Park, Anna Williams, Elise L’Esperance, and George McCoy (the first director of the National Institutes of Health³⁵). Within the next ten years, the membership was to include Karl Landsteiner, Hideyo Noguchi, Karl F. Meyer, Paul DeKruif, and Bela Shick.

AAI was now fulfilling Webb’s and other founders’ earliest vision for the society. The membership was inclusive and flexible, with clinicians, researchers, and public health scientists. With the successful founding of AAI and the preeminence of *The JI*, the standing of immunology as a distinct discipline of science was broadly recognized by the 1920s.

Today, AAI is the largest, most prestigious professional association for immunologists worldwide, with approximately 7,500 members in 60 countries. The society fulfills its founders’ ideals in today’s mission to “promote by its concerted efforts scientific research” in immunology through a dedication to advancing the knowledge of immunology and its related disciplines, fostering the interchange of ideas and information among investigators, and addressing the potential integration of immunologic principles into clinical practice. Since the society’s founding 99 years ago, 19 AAI members have been awarded the Nobel Prize in Physiology or Medicine, 45 have received Lasker Awards, and two have been awarded the Kyoto Prize.

The Journal of Immunology has maintained a level of noted prominence in the field—if not all of bioscience—for almost one century. As the largest journal in the field, it has been dedicated to consistently featuring important and innovative research across a breadth of topics. With over 150 editors and 4,000 volunteer reviewers, *The JI* provides full peer review for the more than 3,500 manuscripts submitted annually.

The AAI annual meeting has evolved from 60 earnest scientists meeting for one day in Atlantic City to over 3,500 scientists meeting for 5 days in selected major cities around the United States. In 2011, 1,768 scientific abstracts were presented; 160 speakers were featured in symposia and other sessions; 130 scientific companies occupied the exhibit floor; and galas, receptions, and parties were held almost every evening.

Every year, hundreds of AAI members work on behalf of their colleagues as members of the Editorial Board of *The JI*, session chairs at the annual meeting, speakers and course instructors, and members or chairs of committees.

The association is overseen by the AAI Council, eight of the most prestigious members, elected to their positions by the membership. The AAI is professionally managed by a hired staff with diverse expertise including scientists who are AAI members.

Each year, AAI gives approximately 500 grants and awards to talented early- and mid-career scientists to cultivate the next generation of leaders and investigators, and AAI recognizes the most senior and accomplished members with a variety of career awards. Through the annual meeting, *The Journal of Immunology*, courses, and the work of its many committees, AAI continues to push forward the boundaries of knowledge in the field and improve the quality of professional life for its members. AAI provides a strong central voice for immunologists, bringing members’ science and issues to the attention of policymakers, funding agencies, and the public.

Not even Synnott could possibly have imagined what that first meeting on a hot summer day in Minneapolis would bring

29. John A. Kolmer, Martin H. Synnott, A. Parker Hitchens, “Resolutions upon the Death of Dr. Richard Weil,” 30 March 1918. AAI Archives.

30. Letter from David J. Kalinski to “Members of the Society for Serology and Hematology” c. 1920. AAI Archives.

31. The actual number of SSH members who joined AAI in 1920 is unclear. The office records state that 19 SSH members joined AAI that year. However, there were an additional 56 eligible SSH members who were provided the opportunity to join, and some of them did, including Elise L’Esperance and future AAI President Lemuel W. Famulener. No official documentation survives for the exact total or dates of election to AAI of the 56 eligible SSH members.

32. Coca, “AFC History beginning of Journal of Immunology.”

33. Minutes of the Meeting of the Council of The American Association of Immunologists, 31 March 1920. AAI Archives.

34. The total membership numbers are the most conservative based on the existing documents in the AAI Archive. Membership in AAI was counted only where election results are verifiable. The most problematic years in reconstructing total AA membership are 1919 and 1920. The AAI council records, which include elections and resignations, from 1919 are completely missing and the records for SSH members joining AAI in 1920 are incomplete.

35. The Ransdell Act (1930) reorganized, expanded, and renamed the Hygienic Laboratory (created in 1887) as the National Institutes of Health. Joseph J. Kinyoun founded and was the first director of the Hygienic Laboratory, serving from 1887 to 1899

Science at the First AAI Annual Meeting

Held in Atlantic City, New Jersey, on June 22, 1914, the small contingent of 18 scientists was a mere handful compared with attendance today, yet the scientific basis of later AAI annual meetings was already evident at this first meeting.

The attendees discussed a diverse range of topics that would help define the new field of immunology. As most of the early AAI members were clinicians, and communicable diseases, which today are easily curable, were still a public health menace, many of the presentations at the meeting focused on public health issues of the time—and, not surprisingly, the topics (and terminology) examined in these early years were rather different from those today. Presentations included examinations of “specific ferments” produced by cells against bacteria, a comparison of available diagnostic tests for syphilis, a study of complement fixation tests to determine the causative bacterium in infective arthritis deformans, and an examination of the intraspinal treatment of syphilis with salvarsan, an organoarsenic and anti-syphilitic compound then in use.

The early science was not without its missteps. The meeting began with several presentations on the Aberhalden Test, a test based on “defensive,” specific proteases formed by exposure of cells to a foreign protein and thought to be diagnostic of pregnancy, infection, and cancer. Although the theory of defensive proteases was not supported by later work, and the pregnancy test developed by Aberhalden was ultimately found to be unreliable, William Whitridge Williams and Clarence B. Ingraham, both of Denver, Colorado, concluded in their presentation on the Aberhalden Pregnancy Test that the test “might be considered a definite and reliable reaction.” However, there was some disagreement among the attending scientists about the nature of the “ferments” produced by cells upon contact with a foreign organism or protein and whether they were in fact protease- or antibody-based.

Other science presented at the meeting perhaps provided a firmer foundation for future work and discoveries in the field. Several scientists, including F. M. Pottenger of Monrovia, California, and Jacob Bronfenbrenner of Pittsburgh, Pennsylvania, gave presentations on the merits of tuberculin therapy—the treatment of tuberculosis with extracts of its bacterial cultures. Although the therapy had not been curative, they debated whether the poor efficacy was a result of differences in animal models vs. human patients or the strain from which the tuberculin was isolated. Although this therapy never became the standard of care, due to inconsistent application and considerable side effects, its deficiencies did inform later immunotherapies for tuberculosis.

Of course, as remains true today, several talks at the meeting dealt with technical innovations, such as a technique for preparing bacterial vaccines pure of extraneous proteins from culture media or a method for culturing infected tissue from arthritis patients.

The scientists at the first AAI annual meeting presented their findings, secure in the knowledge that these studies were of critical import to the future of human health. Gerald B. Webb asserted the importance of the organization and the field in the first AAI Presidential Address when he “agreed with [Sir Almroth E.] Wright that the physician of the future would be an immunologist.”

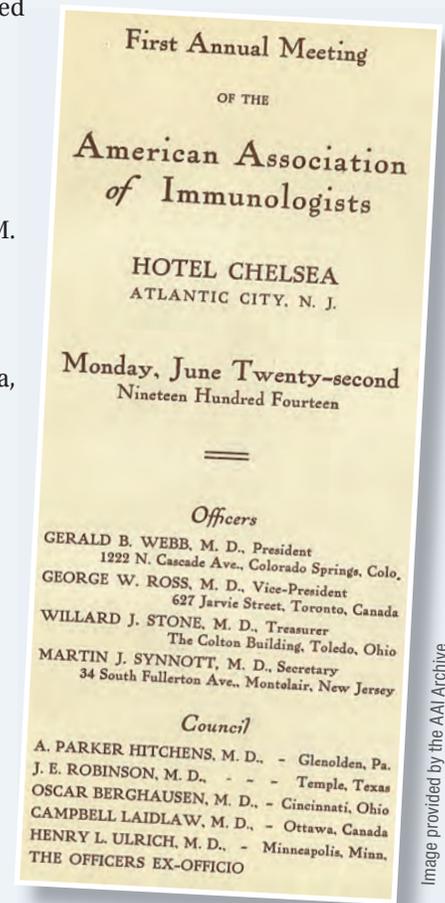
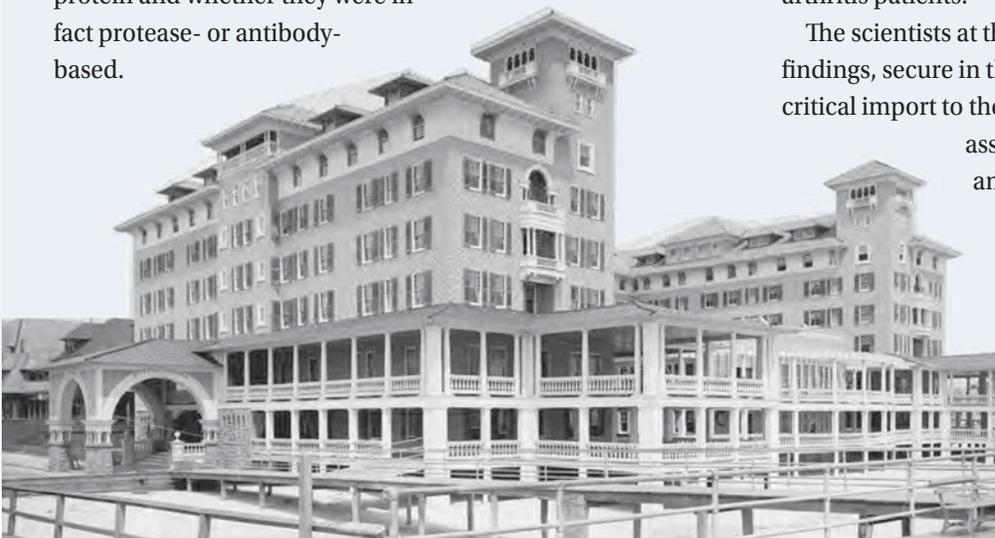


Image provided by the AAI Archive



Hotel Chelsea, Atlantic City, N.J., location of the first AAI annual meeting

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IMMUNOLOGY 2016™: The 100th AAI Annual Meeting

by John Emrich

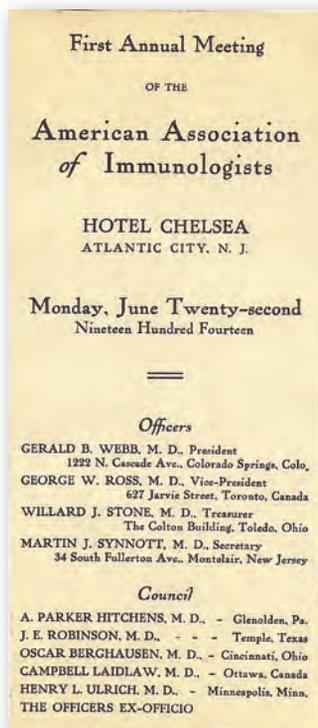
Having Marked Its 100th Anniversary in 2013, AAI Celebrates the Centennials of Its Annual Meeting and The JI in 2016

On a pleasantly warm Monday, June 22, 1914, 40 attendees arrived at the Hotel Chelsea in Atlantic City, New Jersey, for the first annual meeting of The American Association of Immunologists (AAI).¹ This May, 102 years later, the association will hold its 100th annual meeting in Seattle, Washington, with attendance expected to exceed 3,000.

The scientific program for the 100th AAI annual meeting, IMMUNOLOGY 2016™, is to span four full days, with presentations by nearly 100 plenary session lecturers and panelists in major symposia, plus the panelists in 16 guest society symposia, NIH symposia, and career development sessions. Approximately 2,000 scientists at every career stage will present their work in 82 block symposia and poster presentations on 22 abstract topics. In addition to sessions on leading-edge research in established fields, the meeting will feature sessions on emerging fields of immunology and technology. Almost 150 exhibitors will be present to showcase the newest tools and resources available to researchers in the field.

At IMMUNOLOGY 2016™, *The Journal of Immunology (The JI)* will celebrate its own centennial with special exhibits and events and will host its own booth in the Skybridge portion of the AAI Exhibit Hall.

Why is the 2016 meeting in Seattle the 100th annual



AAI Archive, Rockville, MD

meeting if the first was in 1914? A historical hiccup caused by the Second World War is the reason that the AAI annual meeting is currently in sync with the age of *The JI* and not AAI itself. In 1943, 1944, and 1945, wartime travel restrictions in the United States forced the cancelation of national annual meetings for scientific societies large and small, including AAI and all members of the Federation of American Societies for Experimental Biology (FASEB). The AAI meeting in 1943, scheduled to be held in Cleveland, was to be the first annual meeting of AAI as a member society of FASEB, but the meeting was canceled less than one month out. The 1944 and 1945 meetings were also scheduled for Cleveland, but each had to be canceled as well. Since the end of the war, however, all scheduled AAI annual meetings have occurred as planned.

The location of the first annual meeting was determined by the location of the American Medical Association (AMA) meeting, as was the case for the AAI founders' meeting in Minneapolis the previous year.² In that most AAI members were physicians and also members of the AMA, the first AAI Council resolved to hold the smaller AAI meeting one day before the AMA meeting began with its anticipated 4,000 attendees.³ Among the 40 AAI attendees was a particularly engaged Victor C. Vaughan (AAI '15), then



Boardwalk and bathers, Atlantic City, N.J., 1915
Library of Congress Prints and Photographs Division

1. "Today's Sun and Tide Table," *New York Times*, June 23, 1914. The number of attendees at the meeting was calculated using the meeting program, a roll of charter members, and the report of the proceedings in the *Medical Record*. "Society Reports: American Association of Immunologists," *Medical Record* 86, no. 22 (1914): 942-46.
2. For more information about the founding of AAI, see "The Founding of AAI," *AAI Newsletter*, May/June 2012.
3. "M.D.'s at Atlantic City," *New York Times*, June 22, 1914.

the current AMA president. Others in attendance included future AAI Presidents William H. Park and Jacques J. Bronfenbrenner.⁴

A one-hour-long AAI Council meeting preceded the 10:00 AM formal opening of the inaugural annual meeting. The “Address of Welcome” by AAI President Gerald B. Webb was followed by a roll call, an election of officers and members, and the adoption of a constitution and bylaws. Martin J. Synnott, AAI secretary, reported on how the association had been founded and presciently predicted that the AAI would soon be “one of the most important medical organizations on this continent.”⁵

The first scientific session began with George H. Smith of H. K. Mulford Company, Glenolden, Pennsylvania, delivering his paper, “The Production, through Immunization, of Specific Ferments against Bacteria: as Detected by the Abderhalden Test.” The meeting lasted one full day, consisting of three sessions and a total of 19 basic and clinical research talks, including the president’s address.⁶ Each presentation was followed by an open discussion led by an invited scientist.⁷

(To learn more about the science at the meeting, see “Science at the First AAI Meeting,” *AAI Newsletter*, May/June 2012.) At the meeting, the editor of the *Journal of the American Medical Association* requested a report of the proceedings for publication in the journal.⁸

During the next four decades the AAI meeting was held as a stand-alone meeting or concurrently with other societies, including multiple times with the American Association of Pathologists and Bacteriologists (now American Society for Investigative Pathology). Following

the acceptance of membership in FASEB and the resumption of meetings after the Second World War, the AAI annual meeting took place as part of the FASEB annual meeting (now Experimental Biology) from 1946 through 2005 with the exception of eight meetings that were joint meetings with other societies or stand-alone meetings. Since 2005, AAI has held stand-alone meetings, with the exception of its co-location with Experimental Biology in 2008.

Geographically, the AAI annual meetings remained exclusively in the East and Midwest for four decades, with Atlantic City; Philadelphia; New York City; Chicago; Washington, DC; and Toronto each hosting multiple times. In 1955 the first meeting west of the Mississippi River took place in San Francisco. The first meeting in the Pacific Northwest did not occur until IMMUNOLOGY 2000™ in Seattle, but with IMMUNOLOGY 2016™, AAI will have met a third time in Seattle since 2000. The 100 annual meetings have included stops in 27 different cities in 18 states; the District of Columbia; and Ontario, Canada.

More information on the early years of AAI will be featured in the updated AAI Centennial Timeline

to be displayed in the Skybridge portion of the Exhibit Hall at the 2016 AAI annual meeting. Attendees will also be able to view a special exhibit on the first AAI annual meeting as well as the leading immunology scientists and institutions in Seattle. The History Exhibit will be located on the 6th floor of the Washington State Convention Center. ■



Beach and boardwalk, Atlantic City, N.J., c. 1908
Detroit Publishing Company Photograph Collection, Library of Congress

Author: John S. Emrich, Ph.D., *AAI Historian*

Contributor: Charles Richter, *AAI History Intern*

Editor: Mary I. Bradshaw, *AAI Senior Director of Communications and Development*

4. William H. Park was elected in 1916 and served as AAI president in 1918–1919. Jacques J. Bronfenbrenner was elected in 1920 and would serve as AAI president from 1942 to 1946.
5. "Society Reports," 942.
6. Gerald Webb's president's address was "The History of Immunity." The complete text of the address does not seem to have survived, but a description was included in "Society Reports," 945.
7. "Program of the First Annual Meeting of the American Association of Immunologists, June 21, 1914," AAI Archive, Rockville, MD.
8. As AAI did not yet have a journal (*The Journal of Immunology* was first published in 1916), the proceedings of the annual meeting were published in other scientific journals, including the *Medical Record*, *Journal of the American Medical Association*, and the *New England Journal of Medicine*. AAI was required to pay for the publication of the full proceedings but not for summaries of its meetings.

Industry Representation in Early AAI

The American Association of Immunologists (AAI) benefits now, as at its founding, from the participation and contributions of researchers in academia, government, and industry. Although AAI members throughout the association's 102-year history have been based largely in academia, a smaller, but significant, portion of members has worked in government and industry. All three member segments have provided leadership and vision shaping the association of today. In this article, AAI reflects upon the vital contributions of industry members in the organization's first three decades—1913–1943.

These early members were scientists from for-profit, commercial institutions with research laboratories. Some worked in establishments for the medical treatment of people convalescing from a chronic illness and others were employed by pharmaceutical companies.

Of the original 52 AAI charter members in 1913, nine were employed by sanatoria or pharmaceutical companies, including Cragmor Sanatorium, H. K. Mulford Company, and Parke-Davis and Company. By 1943, at least 21 of the then 310 active members had spent at least some of their careers in industry at such companies as Lederle Laboratories, E. R. Squibb & Sons, and Eli Lilly & Company, to name a few.¹

Sanatorium Movement and AAI

In the nineteenth century, tuberculosis remained a leading cause of death in industrialized countries. The disease was, in fact, the leading cause of death in the United States, accounting for one out of every five deaths in the country from 1800–1870. The



Tuberculosis camp in Ottawa, Illinois, ca. 1908

Library of Congress, Prints and Photographs Division

disease afflicted young and old, men and women, urban and rural, and rich and poor.²

The German response to this centuries old scourge was to establish sanatoria predicated upon the importance of “fresh air, rest, good food, and regulated exercise.”³ The first was a private facility was opened by Hermann Brehmer in 1854 in the mountains of Silesia. Because some patients enjoyed dramatic improvement in this setting, the German government funded a number of public sanatoria (Volkshelstätten) in the 1870s.⁴ The ranks of public sanatoria quickly swelled as disability insurance funds became available to fund treatment for most tuberculosis.⁵



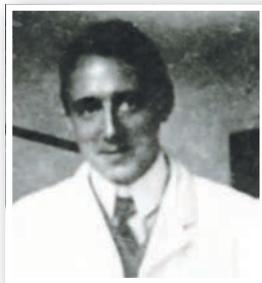
Sanatorium in Lysin, Switzerland, ca. 1890

Library of Congress, Prints and Photographs Division

The emerging U.S. public health movement, coupled with the growing progressive reform movements of the late nineteenth century made the United States fertile ground for sanatoria.⁶ Following New York physician Edward L. Trudeau's opening of his Saranac Lake facility in 1884, a number of U.S. sanatoria were established, albeit with little consensus on effective therapies.⁷ The

1. When the AAI Constitution and Bylaws was adopted in 1917, the only membership category was “Active.” In 1935, an Honorary membership category was created. It was very similar to the current AAI Emeritus member classification.
2. Sheila M. Rothman, *Living in the Shadow of Death: Tuberculosis and the Social Experience of Illness in American History* (Baltimore: The Johns Hopkins Press, 1995), 2.
3. Alan. Kraut, “Plagues and Prejudice,” in *Hives of Sickness: Public Health and Epidemics in New York City*, ed. David Rosner (New Brunswick, NJ: Rutgers University Press, 1995), 77.
4. For more information on the first sanatoria in Germany, see Peter Warren, “The Evolution of the Sanatorium: The First Half-Century, 1854-1904,” *Canadian Bulletin of Medical History* 23, no. 2 (2006): 457–76; Volkshelstätten (“sanatoria for the people”) were also known as Arbeiterheilstätten (“sanatoria for the workers”).
5. Larry Frohman, “Association Prevention, Welfare, and Citizenship: The War on Tuberculosis and Infant Mortality in Germany, 1900–1930,” *Central European History* 39, no. 3 (2006): 441.
6. The terms “sanitarium” and “sanatorium” were used nearly interchangeably in the late nineteenth and early twentieth centuries. The small distinction between the two terms is that sanitariums were generally considered more health retreats/resorts, whereas sanatoria carried more of a hospital connotation. We are using “sanatorium” except when the proper names of an institution dictate the use of sanitarium.
7. Kraut, *Hives of Sickness*, 77.

U.S. sanatoria evolved as three types based on three different funding models: public facilities owned and operated by local or state municipalities; privately funded, non-profit facilities with costs of patient care supported by charitable organizations such as workers' unions or immigrant groups; and private, for-profit institutions to serve the wealthy who could afford to finance their own cutting-edge care.⁸ These sanatoria for the wealthy were among the first to have laboratories,



Gerald B. Webb, 1906
The American Association of Immunologists Collection, Center for Biological Sciences Archive, UMBC

although by the 1910s, most public sanatoria, Catawba Sanatorium in Virginia, for example, included at least a basic laboratory for research.

Two eminent tuberculosis researchers were among the early AAI members associated with private, for-profit tuberculosis sanatoria: the first president of AAI, Gerald B. Webb (AAI '13, president 1913–1915), and Karl von Ruck (AAI '13). Webb lent his national

renown as a tuberculosis physician and researcher to the emergence of Colorado Springs as a center for tuberculosis research and sanatoria.⁹ Having also helped craft the initial scope and membership of the association during the founding meetings, Webb became its first president.¹⁰

Karl von Ruck was founder of the Winyah Sanatorium (1888) and the von Ruck Research Laboratory for Tuberculosis (1895) in Asheville, North Carolina. With both of these institutions playing important roles in establishing that city as a haven for convalescence, the laboratory became a magnet for early-career researchers. Among others there, Jules Freund (AAI '24, president 1955–56) and Louis Dienes (AAI '24), became AAI members soon after their arrival at the von Ruck Laboratory. Both published their clinical and laboratory tuberculosis research in *The Journal of Immunology* (*The JI*).

Other sanatoria-based researchers among early AAI members included Amelia L. Gates (AAI '13), Gates Sanitarium in San Jose, California; Francis M. Pottenger,



Winyah Sanatorium, Asheville, North Carolina
North Carolina Collection Photographic Archives, University of North Carolina at Chapel Hill

Sr. (AAI '13), Pottenger Sanatorium for Diseases of the Lungs and Throat in Monrovia, California; G. Burton Gilbert (AAI '13), Laboratory of the Cragmor Sanatorium, in Colorado Springs; and Silvo von Ruck (AAI '13), Winyah Sanatorium in Asheville, North Carolina.¹¹

Although Webb, as AAI president, held the highest office on the AAI masthead, many sanatoria scientists actively participated in annual meetings, nominated potential new members, and published much of their research in *The Journal of Immunology*, making *The JI* one of the leading repositories of literature on the understanding and treatment of tuberculosis, until the introduction of streptomycin and isonicotinic hydrazide brought the disease under control following the Second World War.¹²

Biologics in Early Pharma

In the early twentieth century, the pharmaceutical industry was undergoing a phase of rapid expansion that coincided with the growth in biologics—and with the founding of AAI. Growth of the largest drug industry trade association provides a useful index to the growth in pharma. That group, the American Drug Manufacturers' Association, was founded in 1912 with 29 companies, but within 10 years, the membership had expanded to 54 companies.¹³

8. *Ibid.*, 77–78. For more information on the German sanatoria system, see Frohman, "Association Prevention, Welfare, and Citizenship," 431–81.

9. For information on how Webb helped Colorado Springs emerge as a center for tuberculosis research and sanatoria, see Helen Clapesattle, *Dr. Webb of Colorado Springs* (Boulder, CO: Colorado Associated University Press, 1984).

10. See "The Founding of AAI," AAI Newsletter (May/June 2012), 24–29.

11. The Gates Sanitarium, founded by Amelia Gates and her husband Howard, was in operation from 1898 through the early twentieth century. The Pottenger Sanatorium for Diseases of the Lungs and Throat, founded by Francis M. Pottenger, Sr. (1869–1961), was in operation from 1903 to 1955. Cragmor Sanatorium, today part of the University of Colorado at Colorado Springs, was founded by Edwin Solly and in operation from 1905 to 1962.

12. Kraut, *Hives of Sickness*, 77.

13. National Association of Manufacturers of Medicinal Products, *Proceedings of the First Annual Meeting*, February 6–7, 1912 (1913), 4; American Drug Manufacturers' Association, *Proceedings of Tenth Annual Meeting*, April 11–14, 1921 (1922), 372–3.

At the time AAI was founded, the expansion of pharmaceuticals was driven by three major currents from the late nineteenth century: the invention of the tableting machine, standardization of drugs by chemical assay, and the first successful use of diphtheria antitoxin and subsequent growth of biologics. Tableting machines ushered in mass production of medications. The use of chemical assays in laboratory testing enabled companies to verify their claims of drug purity.¹⁴ Third, Emil von Behring's discovery of a successful diphtheria antitoxin in 1890 triggered drug manufacturers to enter biologics. Doing so required companies to construct commercial biological laboratories, prompting them either to hire highly trained researchers or associate with a trusted academic or medical institution to guarantee the quality of their products.



Bottle of diphtheria antitoxin, 1895

Images from the History of Medicine, National Library of Medicine

As is the practice today, biomedical researchers moved frequently between academia and the pharmaceutical industry. Scientists commonly split their time equally between positions in industry and academia. Because little data exist on early AAI members' institutional affiliations, it is difficult to determine the length of time an AAI member spent in a particular company. We do, however, know that AAI members who enjoyed some affiliation with the pharmaceutical industry during their careers made contributions, large and small, to shape the association during its formative years.¹⁵



Extraction of diphtheria serum from horse blood, Marburg, Germany, ca. 1895

Images from the History of Medicine, National Library of Medicine

For example, E. C. L. Miller (AAI '13) served on the first nominating committee and recruited three of his former colleagues from Parke-Davis, and John F. Anderson (AAI '18), former director of the Hygienic Laboratory of the United States Public Service (redesignated the National Institutes of Health in 1930), director of the Research and Biological Laboratories, and vice president of E. R. Squibb & Sons, served on

the Board of Editors of *The JI* (1916–1935).

Two early members, Arthur F. Coca (AAI '16) and A. Parker Hitchens (AAI '13), both served as directors at two pharmaceutical companies and left an enduring legacy on the association.



Arthur F. Coca

The American Association of Immunologists Collection, Center for Biological Sciences Archive, UMBC

Arthur Coca was the driving force behind the founding of *The JI* and served as its first and long-time editor-in-chief (1916–1948), serving also on the Board of Editors (1916–1919) and as an assistant editor (1948–1952). It was Coca, who, as president of the New York Society of Serology and Hematology (SSH), laid the groundwork for a "*Journal of Immunity*" and in the spring of 1915, requested the cooperation of AAI in founding a journal for the burgeoning field of immunology. In the fall of 1915, delegations from AAI and SSH reached an agreement to jointly publish the new journal, *The Journal of Immunology*, and unanimously elected Coca as editor-in-chief.¹⁶ As editor-in-chief, Coca guided the journal through the tumultuous editorial and financial problems of its first few decades, establishing the processes and policies that have made *The JI* the pre-eminent peer-reviewed journal in the field. He also served the organization as a councillor (1916–1918), secretary-treasurer (1918–1946), secretary (1946–1948), and, uniquely, honorary president of AAI (1949–1960). During his 43 years of service to AAI, Coca continuously served on ad hoc committees and recruited new AAI members.

Although he began his professional career in academia, Coca is best known for the 18 years (1931–1949) he served as the medical director at Lederle Laboratories. At the time of his arrival to that company, Lederle was producing antitoxins, vaccines, and other biologics. During his tenure there, Lederle developed new biologics, including pituitary and thyroid extracts and sulfa drugs; manufactured penicillin during the Second World War; and isolated and produced the revolutionary antibiotics Aureomycin and Achromycin.

Although not as well known as Coca, A. Parker Hitchens left an equally profound impact on AAI. He served in multiple leadership positions in the nascent years of the

14. Parke-Davis and Company developed the standardization by chemical assay in 1879. Verification by chemical assay was carried out either by the manufacturers in their own laboratories or by associated university laboratories. See Milton L. Hoefle, "The Early History of Parke-Davis and Company," *Bulletin for the History of Chemistry* 25, no. 1 (2000): 30.

15. AAI members in major cities, such as Philadelphia and New York, that had large and small pharmaceutical companies were not included unless they supplied a known street address for a commercial institution. For this reason, all industry member counts are conservative, as we only counted members whom we could conclusively determine worked for a commercial institution.

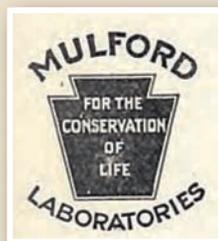
16. For more information on the founding of *The JI*, see "The Founding of *The Journal of Immunology*," *AAI Newsletter* (December 2011), 17–18.

Diphtheria antitoxin and the growth of biologics: Mulford and Lederle Laboratories

In 1890, Emil von Behring announced that he had created a successful diphtheria antitoxin. News quickly made the trans-Atlantic journey and came as a relief to many citizens of U.S. cities, especially New York City. In 1887, one of the largest diphtheria epidemics in the history of the city was responsible for 4,509 deaths.¹ Pharmaceutical companies saw antitoxin as a new opportunity for expansion of their businesses into biologics. H. K. Mulford Company and Lederle Laboratories became large producers of effective diphtheria antitoxins. The two companies, however, achieved their leading market positions by different means.

H. K. Mulford Company

Incorporated in Philadelphia in 1891, H. K. Mulford Company initially mass-produced some 800 different medical products. Their largest seller was a water-soluble pill made possible by their patented tableting machine.² With von Behring's diphtheria antitoxin discovery, however,



H. K. Mulford
Company logo, 1922
from *The Journal of Immunology* 7, no. 4

the owners recognized the potential for a lucrative new venture in biologics. The change in the business model towards biologics required new hires. In 1894 Joseph McFarland, a noted bacteriologist and pathologist at the University of Pennsylvania, became the first major hire for this new endeavor, and a year later Mulford produced the first commercial diphtheria antitoxin in the country.³ The antitoxin was an immediate commercial success and the company quickly began expanding the business to other biologics. This expansion included constructing new laboratories for biological, vaccine, and veterinary research, hiring trained scientists—including physicians, pharmacists, chemists, veterinarians, and botanists—and relocating to a larger property. In 1896 the company moved to a 200-acre farm in Glenolden, Pennsylvania, eight miles outside the city limits, and by 1920 the new site had nearly 1,000 employees and 52 buildings, including stables and barns for the hundreds of horses, cows, and smaller animals.⁴ During the 1920s Mulford specialized in human and veterinary serums, antitoxins, and vaccines, and in 1929 they merged with Sharpe & Dohme, Inc. of Baltimore.

1. Gretchen A. Condran, "Changing Patterns of Epidemic Disease in New York City," in *Hives of Sickness: Public Health and Epidemics in New York City*, ed. David Rosner (New Brunswick: Rutgers University Press, 1995), 31.
2. Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (New York: Cambridge University Press, 1995), 11.
3. Galambos, 13, 17.
4. Galambos 18; Robert F. O'Neil, "Recalling the Heyday of Pioneering Drug Firm the H. K. Mulford Co. of Glenolden Produced a Breakthrough Diphtheria Antitoxin," *Philadelphia Inquirer*, December 27, 1992.

association—first as council chair (1914–1917) and then as a councillor (1918–1921).¹⁷

It was in his role as council chair at the first AAI annual meeting in 1914 that Hitchens became responsible for important facets of organizational governance, including the creation of a constitution and bylaws.¹⁸ It was a responsibility that Hitchens took to heart through the many drafts of each until they were adopted on April 6, 1917. Meanwhile, Hitchens assumed other leadership roles. At the second AAI annual meeting (1915),



A. Parker Hitchens
The American Association of Immunologists Collection, Center for Biological Sciences Archive, UMBC

he was appointed by AAI President Webb to a committee to "influence physicians whose qualifications entitled them to membership in the Association."¹⁹ After membership issues were discussed, Hitchens reported that SSH, led by Arthur Coca, was considering the creation of a *Journal of Immunity* and recommended that AAI help with its founding. In quick order, Hitchens was elected to "represent the society in negotiations with Dr. Coca, with authority to render all possible aid, looking to the publication of the journal."²⁰

17. Council chair was an ad hoc position created in 1913 when AAI was founded. The chair was responsible for the operation of the five-member council—the president, vice-president, and secretary were initially ex officio members of the council. Initially, the council was responsible for considering member nominations, selecting a date and site of the annual meeting, and other general policies, such as determining the amount of the annual dues. When the first constitution and bylaws were enacted in 1917, the position of council chairman was discontinued.

18. The American Association of Immunologists, *Minutes of First Annual Meeting*, June 22, 1914. AAI Archives.

19. Ibid.

20. The American Association of Immunologists, *Minutes of Second Annual Meeting*, 10 May 1915. AAI Archives.

Lederle Antitoxin Laboratories

Lederle Antitoxin Laboratories was founded by former health commissioner of New York City Ernest Joseph Lederle in 1906 to produce diphtheria antitoxin.

Lederle, a trained chemist, had a strong interest in chemical and bacterial testing as it applied to public health and in 36 years at the New York City Department of Health rose in the ranks from milk inspector (1866) to health commissioner (1902). Three years after von Berhing's discovery, Lederle was influential in the creation of the NYC Department of Health bacteriology laboratory under the direction of William Hallock Park (AAI '16, president 1918–1919). The lab focused on methods to identify, control, and prevent communicable diseases.⁵ In 1894, Park and Anna Wessel Williams (AAI '18) isolated the Park-Williams No. 8 strain of diphtheria and used it to create a highly effective antitoxin that was made available to the public the following year.⁶ The antitoxin was produced by the Health Department and provided at no cost to physicians in the city and sold at a nominal cost to health departments in other cities. In 1903, however, with the higher standards of commercial



Diphtheria toxin, Lederle Laboratories, ca. 1951

National Museum of American History, Smithsonian Institution

antitoxins available and pressure from drug manufacturers to cease their anti-free market production, a Health Department directive forced Park's lab to cease production and distribution of the antitoxin.

The following year, 1904, Lederle stepped down as health commissioner after city elections intensified the challenges of the health department's lab, bringing back into power the longtime political machine. Lederle saw opportunity in customers' continuing to request the Park antitoxin following the 1903 interruption in production and resolved to answer the demand. Over the next three years, Lederle recruited scientists and past board colleagues, and, in 1906, founded Lederle Antitoxin Laboratories to produce the diphtheria antitoxin. The new company quickly began taking large orders from across the country. The small and "highly skilled" scientific staff made sure the antitoxin maintained the high standards that Park had produced.⁷ Large sales volumes required an expansion of the laboratories and a relocation from New York City to a 99-acre farm in Pearl River, New York. In those pre-Depression growth years, Lederle Laboratories touted its highly trained scientists working in their modern laboratories to produce bacteriologically sophisticated products.⁸ In the decades that followed, Lederle Laboratories became one of the leading pharmaceutical companies in the United States. Today, after multiple acquisitions, the company is part of Pfizer, Inc.

5. Jonathan M. Liebenau, "Scientific Ambitions: The Pharmaceutical Industry, 1900–1920," *Pharmacy in History* 27, no. 1 (1985): 4; "In Honor of William Hallock Park," *Science* 84, no. 2177 (1936): 261.

6. The Park-Williams strain was also referred to as "American strain #8."

7. Liebenau, 7.

8. Liebenau, 10.

Hitchens was the logical choice. Not only was he a strong advocate for AAI to help found a journal for the field, but also, his involvement in the founding of two other journals, *The Journal of Bacteriology* and *Abstracts of Bacteriology*, gave him insight and experience in the business and editorial management of a new journal. Throughout his professional life, Hitchens continued his service to AAI by helping to organize annual meetings, serving on ad hoc committees, and nominating many future members.

At the time of his involvement in the founding of AAI, Hitchens was biological director of the H. K. Mulford Company. Having joined the company in 1901, as



Package of dried antitetanic serum (ca. 1907) and vial of tetanus antitoxin (ca. 1970)

Images from the History of Medicine, National Library of Medicine

it was expanding research staff to develop antitoxins and vaccines, Hitchens presided over his lab's efforts to develop more effective smallpox and rabies vaccines and production of bacterins and serobacterins and their increases in purity and yield of their diphtheria antitoxin. Hitchens left Mulford in 1918 to enter the U.S. Army Medical Reserve Corps during the First World War and remained in the army as a researcher and teacher for the remainder of his career.²¹

The number of AAI members from industry increased following the Second World War. In 1946, seven of the 37 new members were from the pharmaceutical manufacturers, including American Cyanamid Company,

21. Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895–1995* (New York: Cambridge University Press, 1995), 21–27.

Eli Lilly & Company, and Lederle Laboratories. Throughout the years, the growth and evolution of the pharmaceutical and biotech industry have been reflected in AAI members and leaders. Some, such as Roger M. Perlmutter (AAI '83, president 1999–2000),²² have moved from academia to industry; others, such as Lewis L. Lanier (AAI '80, president 2006–2007),²³ have moved from academia to industry and back again to academia. Today, AAI members in industry participate actively as speakers at the annual meeting, lecturers at the courses, reviewers and editors for *The JI*, and members of various committees. They also serve as mentors to early-career scientists on industry-focused panels and roundtable events at the annual meeting—important resources through which scientists-in-training can explore the variety of opportunities for scientists within industry.

Just how many members AAI may have had from industry is difficult to say. Few AAI members before 1946 provided institutional affiliations, and most changes in institutions were either never recorded or have been lost. There can be little doubt, however, about how AAI has benefited from the participation and leadership of industry members since its founding. ■

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

Katlyn Burns, AAI History Intern, contributed to this article.

22. Roger M. Perlmutter was a professor (1984–1997) and chairman (1989–1997) in the Department of Immunology, University of Washington, before moving into industry. He was previously at Merck Research Laboratories (1997–2001) and Amgen, Inc. (2001–2012) before taking his current position as executive vice president of Merck & Co. and president of Merck Research Laboratories.

23. Lewis L. Lanier began his professional career as a research assistant professor (1981) in the Department of Pathology, University of New Mexico School of Medicine. He then worked for Becton Dickinson (1981–1991) and DNAX Research Institute for Molecular and Cellular Biology, Inc. (1991–1999) before taking his current position as professor, Department of Microbiology and Immunology and the Cancer Research Institute, University of California San Francisco in 1999.

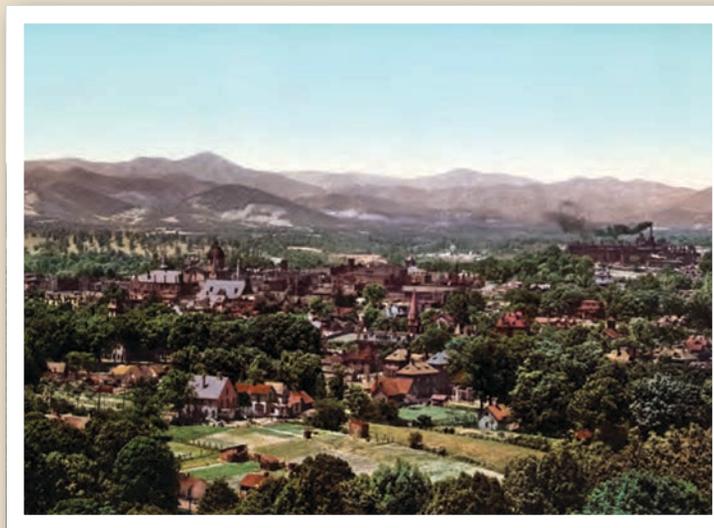
Karl von Ruck: A biographical sketch

Karl von Ruck (AAI '13) was one of the early pioneers of the sanatorium movement in the U.S. Although the movement took many forms, von Ruck was one of the first to build an influential research laboratory alongside his sanatorium to enhance the understanding and treatment of tuberculosis. Born in Istanbul in 1849 to a German diplomat, Karl von Ruck studied under Felix von Niemeyer and graduated with a degree of doctor of medicine from the University of Tubingen in 1877, and, after immigrating to the United States, earned an M.D. from the University of Michigan in 1879. Von Ruck returned to Europe for his post graduate studies, where he conducted research in the laboratories of Rudolf Virchow and Robert Koch—and was present when Koch presented his discovery of the tubercle bacillus on March 14, 1882 at the meeting of the Berlin Physiological Society.¹ After returning to the States, von Ruck spent a few years in private practice in Ohio before focusing exclusively on tuberculosis research. Seeking a more favorable location to conduct research, he decided on Asheville, North Carolina,² in the Blue Ridge Mountains.

In 1888 he established Winyah Sanitarium, one of the first private tuberculosis treatment



Karl von Ruck
North Carolina Collection, Buncombe County
Public Libraries



Asheville, North Carolina
Library of Congress, Prints and Photographs Division, Detroit Publishing Company Collection

institutions in the United States.³ At Winyah, which was closely modeled on German sanatoria, von Ruck believed he could develop a biological means for controlling the disease, including possible immunization. In order to conduct more laboratory research, he established the von Ruck Research Laboratory for Tuberculosis in 1895 on the grounds of Winyah and, in 1910, promoted his son, Silvio von Ruck (AAI '13), to medical director of the hospital thereby freeing his days to focus on research. It was in his laboratory that Karl von Ruck and his colleagues advanced tuberculosis treatment by introducing “the watery extract of tubercle bacilli, a modification of Koch’s fist tuberculin,” and developing a serum “consisting of a protein and lipid extractions of tubercle bacilli

which was used in treatment and with which he hoped to immunize children.”⁴ Patients came from across the country for treatment, including U.S. Senator John W. Kern (D-IN). In addition to creating a pioneering research laboratory, von Ruck founded and co-edited *The Journal of Tuberculosis* with

Silvio and helped establish Asheville as a national center for the treatment of tuberculosis and other respiratory diseases.⁵

Karl von Ruck died in Asheville on November 5, 1922, of complications from chronic nephritis and hypertension.⁶ Both Winyah and the von Ruck Laboratory continued to operate for a number of years after his death,⁷ contributing to his influence in the rapid growth of sanatoria in North Carolina and elsewhere in the South.

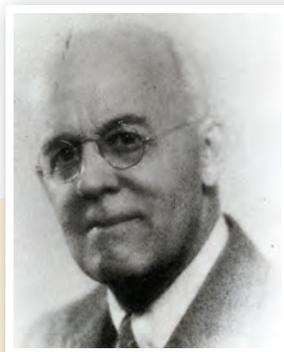
1. Edward W. Shoenheit, “Asheville’s Pioneers: Karl von Ruck, M.D., 1849–1918,” *Chest* 3, no. 6 (1937): 6.
2. In the late nineteenth through early twentieth century, Asheville became a major destination for convalescing patients. It was believed that the clean mountain air, altitude, and temperate climate had healing properties. The first privately operated tuberculosis sanatorium opened in Asheville in 1871.
3. “Dr. Carl von Ruck Dies,” *New York Times*, November 7, 1922.
4. Shoenheit, 6; In 1913 the von Rucks unsuccessfully campaigned to have the Public Health Service verify what they maintained was a serum for treating tuberculosis. See “Biographical Note,” Karl and Silvio von Ruck Papers 1907–1915, National Library of Medicine, Bethesda, MD
5. Shoenheit, 24; *The Journal of Tuberculosis* was published from 1899 to 1903 in Asheville, N.C.
6. Shoenheit, 24.
7. The closing dates for Winyah Sanitarium and the von Ruck Laboratory could not be determined.

Founding *The Journal of Immunology*

by John Emrich

The year 2016 marks the centennial year for *The Journal of Immunology* (*The JI*), the preeminent peer-reviewed journal in the field of immunology and the official publication of The American Association of Immunologists (AAI) since 1916. Though long “the jewel in the crown” for AAI, *The JI* did not receive its genesis from within the AAI membership or Council. The request for creation of the journal, in fact, arose from within another society. Thanks to the foresight and organizational skills of A. Parker Hitchens, a founding member and the first chair of the AAI Council, the journal received its association with AAI.¹

When AAI, in 1915, was presented the opportunity to help found a journal, leaders of the burgeoning professional society were still focused on developing the membership and drafting bylaws. No mention of founding a journal dedicated to immunology appears in the minutes from either their organizational meeting in 1913 at the American Medical Association meeting in Minneapolis, Minnesota, or the first annual meeting in Atlantic City, New Jersey, in 1914. As was the case for many other small societies, the publishing activities of AAI were limited to publishing reports of its meetings in the journal of a larger society. (AAI published its first five annual meeting proceedings in the *New England Journal of Medicine* and *Journal of the American Medical Association*.²) The focus of the AAI Council changed quickly, however, in the spring of 1915 with a request from Arthur F. Coca, president of the New York Society for Serology and Hematology (SSH).



Arthur F. Coca
The American Association of Immunologists, Center for Biological Sciences Archive, UMBC

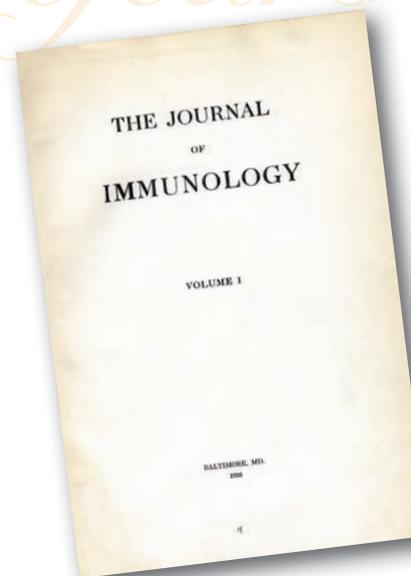
Arthur F. Coca, M.D. (1875–1959), elected to AAI in 1916, was the founder of *The Journal of Immunology* and served as its Editor-in-Chief from 1916 to 1948. In 1949, Coca was named honorary president of AAI, a title that has remained uniquely his through the years. Coca was a faculty member at Cornell University Medical College from 1910 to 1931,

Coca, instructor in pathology and bacteriology at Cornell University Medical College, was spearheading a movement to establish a “Journal of Immunity” modeled on the German journal *Zeitschrift für Immunitätsforschung und experimentelle Therapie*.³

Recognizing a potential synergy with the goals of the AAI, Coca reached out to the members of the AAI Council to determine if the society would consider cooperating in founding the journal. It was not wholly surprising that the two societies should cooperate, as they shared many members, and Coca was himself nominated for membership in AAI in 1915.

In his communications with Coca, Hitchens became convinced that a journal “devoted to the branch of medical science represented

attaining the position of full professor in 1924. In 1931, Coca accepted positions as professor of medicine at the New York Postgraduate Medical School at Columbia University (1931–1935) and as the medical director at Lederle Laboratories. He remained at Lederle Laboratories until his retirement in 1949.



***The Journal of Immunology*, Volume 1, No. 1**
The American Association of Immunologists Archive

1. Before the adoption of the Bylaws and Constitution in 1917, authored by A. Parker Hitchens, the American Association of Immunologists was governed by the president and the Council. The early Council included the position of chair, responsible for making sure the Council carried out its proposals and those of the president. The early Council did not have a line of succession to the presidency, as it would after 1917.
2. “Minutes of First Annual Meeting of the American Association of Immunologists,” June 22, 1914, AAI Archive, Bethesda, MD [hereafter, AAI Archive-Bethesda]. Both the *New England Journal of Medicine* and *Journal of the American Medical Association* regularly published meeting reports and proceedings of smaller scientific and medical associations.
3. A. Parker Hitchens, “Report upon *The Journal of Immunology*,” Annual Council Meeting, June 10, 1916, AAI Archive-Bethesda. *Zeitschrift für Immunitätsforschung und experimentelle Therapie* was first published December 1908.

by this Association was about to be established” with or without any involvement of AAI. It was also clear to Hitchens that Coca’s work on establishing the new journal had progressed far enough that the inaugural issue would be published before the AAI Council could act on any potential arrangement. Furthermore, if such a journal was published without the cooperation of AAI, it would render “superfluous the future publication of an official organ of this Association, and, in this event, our Society would have been seriously handicapped in its future development.”⁴

Hitchens formally presented the idea of the “Journal of Immunity” to Council when it convened in early May at the annual meeting. Most councillors were receptive to the new journal and “thought it a good thing and that the society should cooperate with Dr. Coca in the matter.”⁵ Although Council could not be expected to take decisive action immediately on a matter of such consequence, the Council members empowered Hitchens “to represent the society in the negotiation with Dr. Coca”⁶ and act for the Council in any negotiations.⁷ In Hitchens, the Council could not have made a more apt selection. He was the

“[I am] of the opinion that there are enough journals now.”

—James W. Jobling, AAI president, August 5, 1915

secretary of the Society of American Bacteriology (SAB, now the American Society for Microbiology) and would soon be the first managing editor of the newly founded *Journal of Bacteriology*

(*JB*) as well as the first and only editor of *Abstracts of Bacteriology*.⁸ Furthermore, he negotiated the *JB* contract on behalf of SAB with the publisher Williams & Wilkins Company of Baltimore.⁹ Despite these crucial early decisions by Hitchens and the AAI Council, it was not a certainty that *The JI* would be the official publication of the association.

The full AAI leadership was not completely convinced of the need for a new journal specializing in immunology. In August, new AAI President James W. Jobling, M.D., professor of pathology at Vanderbilt University, wrote to his past colleague Simon Flexner, director of the prestigious Rockefeller Institute of Medical Research (RIMR), expressing his reservations about the prospects of a new journal.¹⁰ Flexner was an understandable choice, as the renowned William H. Welch had recently transferred ownership and publication of the

1920 for an appointment at the Hygienic Laboratories of the Public Health Service, now the National Institutes of Health, before returning to the Medical Corps, where he remained until his retirement from the Army in 1941 as a lieutenant colonel. He spent the last four years of his professional career in public service, working for municipal and state boards of health.

Arthur Parker Hitchens, M.D., (1877–1949) was a founding member of AAI and served in a number leadership positions in the earliest years of the association—first as council chair (1914–1917) and later as a councillor (1918–1921). Hitchens was a staff scientist at H. K. Mulford Company from 1901 until 1918, when he joined the U.S. Army Medical Corp for service in the First World War. Hitchens left the Army for a short time in



A. Parker Hitchens
The American Association of Immunologists, Center for Biological Sciences Archive, UMBC

4. Hitchens, “Report upon *The Journal of Immunology*,” 1916, AAI Archive-Bethesda.
5. “Minutes of Second Annual Meeting of the American Association of Immunologists,” May, 10 1915, AAI Archive-Bethesda.
6. Ibid.
7. Hitchens, “Report upon *The Journal of Immunology*,” 1916, AAI Archive-Bethesda.
8. Arthur Parker Hitchens, M.D. (1877–1949), was the secretary-treasurer for the Society of American Bacteriology (SAB) in the 1910s and 1920s. He also served as vice president (1923) and president (1924) of SAB. The SAB was renamed the American Society for Microbiology in December 1960. The *Journal of Bacteriology* was first published in January 1916 and continues today. *Abstracts of Bacteriology* was published from February 1916 until December 1925.
9. Claude P. Brown, “Arthur Parker Hitchens, 1877–1949,” *Journal of Bacteriology* 60, no. 1 (1950): 2.
10. The Rockefeller Institute of Medical Research (RIMR), which opened in 1901, was renamed The Rockefeller University in 1965. Simon Flexner was the first director of RIMR and held the position until 1935.

prestigious *Journal of Experimental Medicine* to RIMR, with Flexner serving as editor, a role he was to fulfill from 1905 to 1946.¹¹ Though the proposed immunology journal would be “international in character,” Jobling had his doubts that “it would receive sufficient support to justify its existence.” Furthermore, he was “of the opinion that there are enough journals now.” Despite the compelling reasons stated by proponents, Jobling was demonstrably opposed to “any idea leading to the financial responsibility” on the part of the nascent association for fear that initial costs might place serious strain on the finances of the young society.¹²

Jobling, however, chose not to make the long train trip from Nashville, Tennessee, to attend a joint meeting of the councils of AAI and SSH at the new Yale Club in New York City on October 7, 1915. The meeting was scheduled for leaders of the societies to explore production requirements and consider a working relationship for the proposed new journal, now dubbed the “Journal of Immunology.” The AAI Council was represented by Council Chair Hitchens, Vice President George P. Sanborn, Councillor John A. Kolmer, and Secretary Martin J. Synnott. In addition to President Jobling, three councillors and the treasurer elected to miss the meeting.¹³ To ascertain the costs associated with the proposed journal, Coca invited representatives from the publishing services company, Williams & Wilkins. The meeting resulted in a positive prospect for the publication of the journal: Coca was

unanimously elected managing editor;¹⁴ a committee to select the board of editors was created; and the advisory board began taking shape.¹⁵

Despite these positive developments, a large, unresolved issue still loomed over the AAI delegation: how was the society to finance its portion of the publishing costs?

Resources were scarce. AAI Treasurer Willard J. Stone, in a December 28, 1915, letter to Martin Synnott, estimated the association’s portion of the publishing expenses for the first year at \$240, an amount exceeding available funds in the treasury by \$75.¹⁶ With just 58 members, AAI would have to assess each member \$4.00 in addition to their \$5.00 annual dues assessment to cover costs. In addition to imposing such a high fee on member subscribers, the two societies would be required by Williams & Wilkins to cover the deficit guarantee in case sufficient subscription revenues were not reached. The two-and-one-half year-old AAI was in no position at the time either to offset the high subscription fee for members or cover the deficit guarantee required by Williams & Wilkins.

AAI was also constrained from raising dues to expand its financial reserves. The just-drafted bylaws stated, “The dues of the Association shall be fixed annually by the Council and they shall not exceed five dollars.”¹⁷ Although Council soon realized that this cap could not be maintained indefinitely, the \$5.00 maximum



James W. Jobling, c. 1915
The American Association of Immunologists, Center for Biological Sciences Archive, UMBC

James W. Jobling, M.D. (1876–1961), elected to AAI in 1914, served the association as its second president (1915–1916) and as a member of *The Journal of Immunology* board of editors from 1916 to 1935. Before his election to AAI, Jobling had worked as a pathologist at Michael Reese Hospital in Chicago from 1909 until moving in 1913

to join the faculty of Columbia University College of Physicians and Surgeons (P&S) as an assistant professor. In 1914, Jobling left P&S to accept a post as full professor of pathology at Vanderbilt University School of Medicine. In 1918, he returned to P&S as professor of pathology, a position he held until his retirement in 1945.

11. Welch founded and edited the *Journal of Experimental Medicine* from 1896 to 1902. He transferred the journal to RIMR in 1902, and publishing was suspended until 1905, as the backlog of all submitted manuscripts needed to be moved from Baltimore and organized and reviewed at RIMR. The position of editor was similar to editor-in-chief today.
12. James W. Jobling to Simon Flexner, August 5, 1915, Simon Flexner Papers, “Jobling, James W., 1912–1945, Folder 1,” American Philosophical Society, Philadelphia, PA.
13. Absent from the meeting were Treasurer Willard J. Stone and Councillors Oscar Berghausen, Campbell Laidlaw, and Henry L. Ulrich. Minutes of joint meeting of AAI and SSH Councils, 7 October 1915, AAI Archive-Bethesda.
14. The position of managing editor was the equivalent to editor-in-chief today.
15. Minutes of joint meeting of AAI and SSH Councils, October 7, 1915, AAI Archive-Bethesda.
16. The current balance of the treasury was estimated by Stone to be around \$165. Willard J. Stone to Martin J. Synnott, 28 December 1915, AAI Archive-Bethesda.
17. The AAI Constitution and Bylaws were ratified in 1917 without an explicit maximum of dues. The proposed Constitution and Bylaws were unanimously adopted at the first annual meeting of the American Association of Immunologists, June, 22 1914; Hitchens, “Report upon *The Journal of Immunology*,” 1916, AAI Archive-Bethesda.

for dues stood as an unofficial ceiling into the 1920s. By providing the official journal of the society to members within their dues, as was typical of learned societies, only \$1.00 of income per member would remain for maintenance of AAI activities. Council members knew that was an insufficient amount “for the maintenance of the Society’s affairs,”¹⁸ notably the annual meeting, which cost the association nearly \$200 in 1915.¹⁹

Hitchens, however, was able to address both financial challenges without putting the association in financial straits. He proposed making journal subscriptions optional for AAI members and providing members a 20 percent discount on their subscriptions, charging members \$4.00 annually, compared to the \$5.00 assessed non-members in the United States to subscribe.²⁰ To address the deficit guarantee, he sent out personal letters to “several of the more interested members, offering them the privilege of guaranteeing individually a fraction” of the fund. He quickly received enough positive responses to “assure the publishers of adequate financial support to proceed with the Journal.”²¹

There is no record of the AAI Council holding an official vote approving publication of

SUBSCRIPTION TERMS

The Journal of Immunology will be a bimonthly. Each volume will consist of six numbers and will contain from 500 to 525 pages. The subscription price is \$4.00 to members of the American Association of Immunologists and the New York Society of Serology and Hematology; \$5.00 to non-members in North America; \$5.50 elsewhere. Postage free. Subscriptions and all business matters should be sent to the Williams & Wilkins Company, 2419–21 Greenmount Avenue, Baltimore, U. S. A.

Subscription Terms for *The Journal of Immunology*, 1916
The American Association of Immunologists Archive

The JI, but President Jobling, during the annual meeting May 11–12, 1916, sent a letter to all AAI members urging them to subscribe to the new journal “devoted to the problems of Immunology.” In the letter, Jobling described the policy of the journal as “to welcome all studies bearing on

the general problems of Immunology as well as to publish the proceedings of our association.”²²

The inaugural issue of *The JI* was published in February 1916 as a cooperative effort between AAI and the New York Society of Serology and Hematology. The bimonthly journal would serve as the official organ for both organizations. It would also provide demarcation of immunology as a separate field in the medical community and create a locus for immunological research from “the best equipped laboratories in this country and England.”²³

The first issue of the new journal contained articles on mechanisms of anaphylaxis and immunity and viral and bacterial infections, as well as the scientific proceedings of the December 3, 1915, meeting of SSH. The first article was “Studies in Anaphylaxis: On the Relation between Precipitin and Sensitizin,” by Richard Weil, chair of the Department of Experimental Medicine at Cornell Medical College. In the article, Weil, a founding member

Richard Weil, M.D. (1876–1917), elected to AAI in 1914, served the association as its third president (1916–1917), councillor (1917), and member of *The Journal of Immunology* (*The JI*) Board of Editors (1916–1917). A faculty member at Cornell University Medical College from 1911 until his premature death in 1917, Weil wrote the first article published in *The JI*, the 14th part in his 17-part “Studies in Anaphylaxis”



Richard Weil, c. 1915
The American Association of Immunologists, Center for Biological Sciences Archive, UMBC

series. Weil proceeded to publish parts 16 and 17 of this series in *The JI*. Commissioned into the U.S. Army Medical Corp when the United States entered the First World War in 1917, Weil was appointed chief of medical staff at Camp Wheeler near Macon, Georgia. While attending hospitalized troops there, Weil contracted pneumonia and died on November 19, 1917.

18. A. Parker Hitchens to Martin J. Synnott, February 9, 1916, AAI Archive-Bethesda.

19. Willard J. Stone to Martin J. Synnott, December 28, 1915, AAI Archive-Bethesda.

20. The subscription price for non-members outside of the United States was \$5.50.

21. Hitchens, “Report upon *The Journal of Immunology*,” 1916, AAI Archive-Bethesda.

22. James W. Jobling and Martin J. Synnott to AAI membership, May 11 and 12, 1915, AAI Archive-Bethesda.

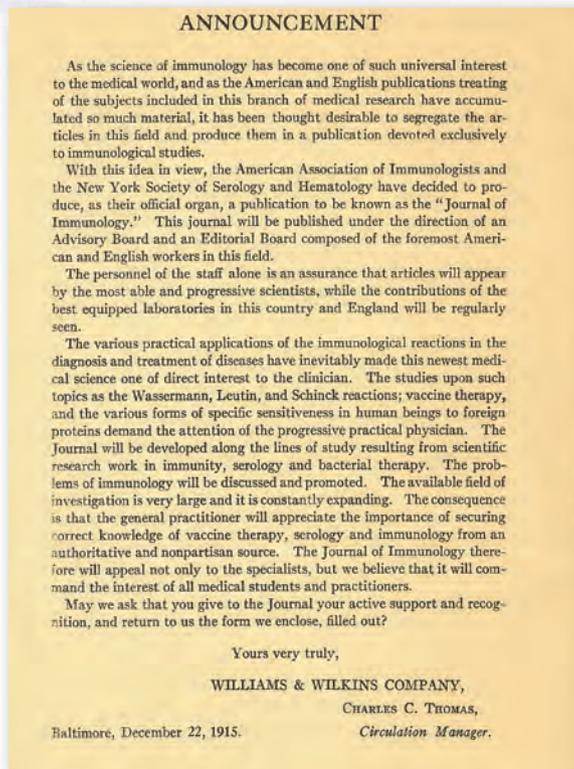
23. Announcement of *The Journal of Immunology*, 1916, AAI Archive-Bethesda.

of AAI, a member of SSH, and a member of the board of editors of *The JI*, took a firm stance on the cellular cause of anaphylaxis at a time when the mechanism was hotly debated.

Thirteen months later, Charles Thomas, circulation manager of Williams & Wilkins, sent the AAI Council a promising status update on the new journal. The subscription list of *The JI* had grown to 439 with subscriptions “received from practically every foreign country,” except those of the Central Powers countries of the First World War.²⁴

The average number of new subscribers each month had increased to 20 since November 1916, and Thomas predicted that subscriptions should reach 550–600 by the end of the year. His final assessment of the new journal was that it “has a fine future and that it will establish itself on a substantial basis, taking care of its own expenses.”²⁵

On March 31, 1920, the AAI Council and SSH Executive Committee met at the home of AAI and SSH President Hans Zinsser in New York City.²⁶ As SSH “had omitted its monthly meetings for over a year and since the functions of the society had been in a measure superseded by the American Association of Immunologists,” the society wished to merge with AAI. An agreement was reached between the two organizations, and the proposal was put before the SSH membership that summer. On July 27, 1920, a quorum of SSH members voted in the



Announcement of *The Journal of Immunology*, 1916
The American Association of Immunologists Archive

“I believe that my interest in this direction is engendered by my desire to see the Association of Immunologists on a good, sound and influential basis.”

—A. Parker Hitchens, February 9, 1916

affirmative that all members in good standing were to be notified that they would become members of AAI unless they had “definite objections.” By the end of the year, SSH had ceased operations, and all but a handful of their members had joined AAI. With the cessation of SSH, AAI became the sole publisher of *The JI*.²⁷

Over the years, *The Journal of Immunology* has published many influential articles that have moved the field of immunology forward. In the process, it has fulfilled, if not surpassed, Hitchens’s expressed wishes for the role to be played by the journal: “I believe that my interest in this direction is engendered by my desire to see the Association of Immunologists on a good, sound and influential basis. As I see it, the position I am anxious to have the Association take can scarcely be gained unless the Association has an official organ.”²⁸

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

Contributor: Kaylene J. Kenyon, Ph.D.,
The Journal of Immunology
AAI Publication Director

Editor: Mary I. Bradshaw, M.A., M.Ed., AAI Senior Director
of Communications and Development

28. The Central Powers included Germany, Austria, Hungary, Bulgaria, and Ottoman Empire. By March 1917, the war had already been raging across Europe, Russia, and Anatolia for two years and nine months.

29. Charles Thomas to Martin J. Synott, March 30, 1917, AAI Archive-Bethesda.

30. Hans Zinsser, M.D. (1878–1940), was elected to AAI in 1917, served as its sixth president (1919–1920), and was a member of the board of editors of *The Journal of Immunology* (1916–1940).

31. David J. Kalinsky, secretary of SSH, to the Members of the Society for Serology and Hematology, draft, 1920, AAI Archive-Bethesda.

32. A. Parker Hitchens to Martin J. Synnott, February 9, 1916, AAI Archive-Bethesda.

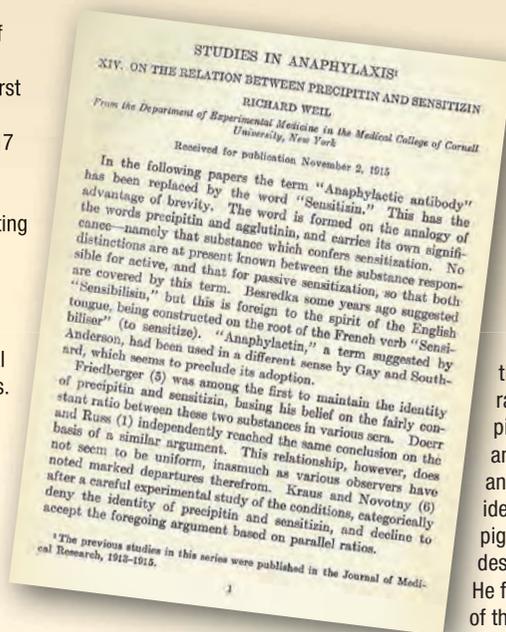
The First Article in *The Journal of Immunology* “Studies in Anaphylaxis”

In February 1916, The American Association of Immunologists and the New York Society for Serology and Hematology jointly published the first issue of *The Journal of Immunology*. (See “The Founding of *The Journal of Immunology*”, page 17 of this newsletter) The goal for the new journal was to advance the field of immunology, already recognized to be vital to understanding and treating disease, by publishing the newest research in “immunity, serology, and bacterial therapy” and discussing the “problems of immunology.”¹ With these aims in mind, the editors chose for the first article a study on a major immunological debate of the day, the mechanism of anaphylaxis.

The article was “XIV. Studies in Anaphylaxis: On the Relation between Precipitin and Sensitizin” by Dr. Richard Weil, chair of Department of Experimental Medicine, Cornell Medical College.² The article is of interest for more than just its scientific content as it also demonstrates the scientific milieu and conventions of the time. Weil was well placed to publish his paper, for he was a founding member and future president of The American Association of Immunologists and also a member of the New York Society for Serology and Hematology. Unlike most modern research papers, his article had only a single author, lacked defined Abstract, Methods, Results, and Discussion sections, and was written in an almost conversational style. Further, the article was the 14th in a series, with the first 13 published in the *Journal of Medical Research* — the 15th, 16th, and 17th (the final) in the series were published simultaneously with the 14th in *The JI*. In this first *JI* article, and throughout his larger series of articles, Weil persuasively argued for a cellular mechanism of anaphylaxis.

Although the phenomenon of anaphylaxis had been described earlier, the seminal experiments were reported by Richet and Portier in 1902. In attempting to vaccinate experimental animals including pigeons and dogs against the toxin of the Portuguese man-of-war or, later, sea anemones, they were shocked to note the opposite effect. The animals injected with a second vaccinating dose became violently ill and died. Richet and Portier created a new term for this observed hypersensitivity: “anaphylaxis,” which literally means “against protection.” Following previous demonstrations of natural and artificially induced immunity to infection, the description of anaphylaxis was the first comprehensive demonstration of harmful effects caused by the immune system. This discovery changed the conception of immunology and earned Richet the Nobel Prize in Physiology or Medicine in 1913.

By the time of the publication of Weil’s article in *The JI*, scientists were divided in their views on whether the cause of anaphylaxis was humoral or cellular — a divide firmly entrenched in early immunology itself. While both sides agreed that interaction between antigen and antibody caused anaphylaxis, proponents of the humoral theory asserted that antigen and antibody combined in the blood to form a chemical toxin. In his Nobel address, Richet touched upon this idea as a simple explanation for the ‘toxin’ produced by *in vitro* incubation of immune serum and antigen. He explained that “there exists in anaphylactized blood a substance harmless in itself but which releases a strong poison when mixed with the antigen.”³ Weil was unconvinced that events in a test tube emulated the situation *in vivo* and was one of the first



supporters of the cellular theory. This theory hypothesized that antibodies became bound to cells and that antigen-antibody binding induced the cell to produce the anaphylactic reaction. In a talk in January 1916, just prior to publication of his article in *The JI*, he stated that the difference between these two theories was not “merely scholastic,” but that the “entire philosophy of immunity is involved in the choice between them.”⁴

In Weil’s article, he described how, through a series of injections of immune rabbit serum and horse serum into guinea pigs, he concluded that “precipitating antibody” and “sensitizing antibody” (i.e., antibody responsible for anaphylaxis) were identical. (Interestingly, by studying the guinea pig as a model, he primarily would have been describing IgG1, rather than the classic IgE.) He further stated that the precipitating function of the antibody could be destroyed (by heat or chemical treatment) without affecting the sensitizing value, presuming this to be due to the retained antigen-binding capacity of the antibody. In his concluding statements, Weil firmly asserted his belief regarding the mechanism of anaphylaxis: “Anaphylaxis therefore consists simply in the cellular reaction due to the fixation of antigen by cellular antibody.”

Of course, we know today that Weil would ultimately be proven correct in his cellular theory of anaphylaxis. The discovery of IgE in the 1960s spurred impressive progress in the field. It is now well established that antigen crosslinking of IgE on mast cells and/or basophils triggers their degranulation to induce anaphylaxis and that prompt treatment with epinephrine reverses the life-threatening effects. Nevertheless, the frequency of anaphylaxis seems to be increasing, and patients look toward current researchers for new solutions. A century following the experiments of Richet and Weil, investigators continue to shed light on signaling events which occur during anaphylaxis, identifying potential new therapeutic targets.

From its launch in February 1916, *The JI* was intended to advance the field of immunology as a whole. But the editors of the journal and, by extension, the members of AAI also wanted to represent the contributions of preeminent scientists in the U.S. and England in particular. Given their attempt to define themselves as a group, their choice of the first article was perhaps not so surprising. The publication of Weil’s article placed *The JI* on one side of a hotly debated issue, ensuring the relevance of the journal to the field and positioning the young society as an emerging forum for discussion and dissemination of discoveries advancing immunology.

¹ Announcement. *The Journal of Immunology* vol. 1.

² Richard Weil, “Studies in anaphylaxis. XIV. On the relation between precipitin and sensitizin,” *The Journal of Immunology* vol 1 (1916): 1–18.

³ Charles Richet, “The Nobel Prize in Physiology or Medicine 1913 - Award Ceremony Speech,” Nobelprize.org, http://nobelprize.org/nobel_prizes/medicine/laureates/1913/press.html (accessed August 10, 2011).

⁴ Richard Weil, “Anaphylatoxin and the mechanism of anaphylaxis” in *Proceedings of the second Pan American scientific congress*, vol 10, sec 8, part 2, ed. Glen Levin Swiggett (Washington, DC, GPO, 1916), 308–313.

In preparation for IMMUNOLOGY 2015™ in New Orleans, Louisiana, the history of AAI members and institutions in the state was researched for a special exhibit at the meeting. In the process, the story of Charles C. Bass's colorful career, recounted below, emerged as among those worthy of a wide audience. More information on the biomedical history of Louisiana will appear in the next AAI Newsletter.

Country Doctor, Pioneering Parasitologist, and the Father of Preventative Dentistry

Charles C. Bass, M.D. (1875–1975)

by John Emrich

Charles Cassidy Bass (AAI '16), the first member of the American Association of Immunologists (AAI) in Louisiana, began his medical career quietly as a country doctor but rose to prominence and acclaim, not only in his studies of diseases endemic to the American South but also in his pioneering post-retirement research establishing the field of preventative dentistry.

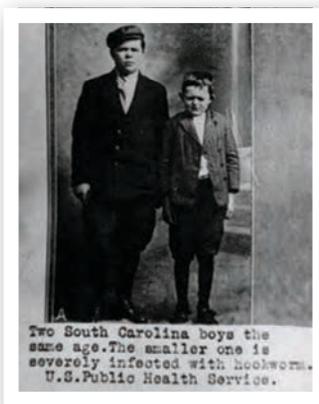
In addition to his research, Bass's renown stems from his eventful 18 years as dean of Tulane University School of Medicine. During his tenure at Tulane, Bass modernized the medical school, doing so despite resistance from the then extremely powerful populist Louisiana Governor Huey Long.

The Country Doctor

Bass was born January 29, 1875, on the family farm in Carley, Marion County, Mississippi.¹ After high school, Bass spent two years working on the farm before entering (1896) and graduating (1899) from Tulane University School of Medicine. Bass then returned to Marion County as a family physician. As the youngest of three physicians in Columbia, Mississippi, Bass had an unremarkable start to his medical



Charles C. Bass
*Images from the History of Medicine,
National Library of Medicine*



*Images from the History of Medicine,
National Library of Medicine*

career. During his first four years of practice, he was a typical country doctor, operating a small practice out of his home and regularly making house calls on horseback.² His career, however, changed dramatically when he attended a 1903 American Medical Association meeting in New Orleans.

At the meeting, Bass heard a number of lectures on hookworms. The majority of the speakers agreed on two things: a parasite was responsible for hookworm disease (also known as uncinariasis), and the disease was new to the United States. One talk in particular caught Bass's attention when the speaker argued that hookworm infections rarely, if ever, occurred in this country. Bass knew empirically that this statement was wrong. He had seen many of his own patients, especially children, suffering from the exact symptoms described by the speaker.³ Shortly after the meeting, he purchased a microscope and, over the next seven to eight months, began testing the children of Marion County for hookworm.⁴ By the end of his study, he had identified and treated 75–80 cases of hookworm.⁵ Bass became so engrossed in laboratory research that in 1904, he enrolled in a one-year-long course in clinical laboratory diagnosis at

1. Rudolph Matas, *Dr. Charles C. Bass, Dean: An Appreciation* (New Orleans, LA: Tulane University School of Medicine, 1940), 2. Originally published in *New Orleans Medical and Surgical Journal* 92, no. 10 (1940): 545–50.

2. Arden G. Christen, "Charles C. Bass, M.D.—1875–1975: That Cantankerous Genius of Preventative Dentistry," *Bulletin of the History of Dentistry* 30, no. 1 (1982): 9.

3. Most people infected with hookworms have no symptoms. Minor symptoms include gastrointestinal problems. In serious cases, there is blood loss, leading to anemia and protein deficiency. In children with continuous infection, the loss of iron and protein results in growth and developmental problems.

4. Matas, *Dr. Charles C. Bass*, 5–6.

5. Matas, *Dr. Charles C. Bass*, 6.

the Johns Hopkins University. At Johns Hopkins, he studied microscopy under Charles E. Simon and the proper techniques for blood counts under William S. Thayer.⁶

Following his training at Johns Hopkins, Bass chose not to return to his family practice in Columbia. Instead, he relocated with his family to New Orleans, where he started a new practice. He saw patients in a conventional medical office building but constructed his own personal laboratory at home.



Tulane University School of Medicine, Canal Street, c. 1900
Library of Congress, Prints and Photographs Division

Research Pioneer

Bass's home research did not go unnoticed by his alma mater, Tulane. In 1905, he was appointed to a non-salaried position as an instructor in the Department of Medicine, and in 1907, he was hired as a salaried instructor of clinical microscopy and medicine in the Tulane laboratories of clinical medicine.

Interested in opsonic index and autogenous vaccines, Bass traveled to England in 1908 to train with Sir Almroth Wright (AAI '14), an early authority

on inoculation techniques and vaccine therapy, at St. Mary's Hospital.⁷ The work he undertook in England helped to form his later research, and the relationships he built there with the future founders of AAI led to his nomination and election to the association in 1916.

Back in the States, Bass was soon promoted to director of the Tulane laboratories and, in 1912, to professor of experimental medicine. While in the laboratories of clinical medicine, Bass immersed himself in uncinariasis and defined the etiology, pathology, and more effective treatment for the disease.⁸

His pioneering work in this area was based on a small study of 90 students at Tulane. He discovered that, whereas 20 percent of all participants were suffering from uncinariasis, 42 percent of the rural students carried the parasite.⁹ In 1910, he published findings from a large study conducted with George Dock, in which they were the first to assert that the high rate of infection in the rural South was attributable to sandy soil, the poor access of privies, and the "habit among children...of going barefoot."¹⁰

While completing his research on hookworm infections, Bass began studying another parasitic disease afflicting the South: malaria.¹¹ In 1911, he successfully cultivated the three most common malarial plasmodia (vivax, malariae, and falciparum) in vitro using human blood and published a seminal paper, entitled "A New Conception of Immunity: Its Application to the Cultivation of Protozoa and Bacteria from the Blood and to Therapeutic Measures."¹² This breakthrough in hematic



Patient with a hookworm infection
Centers for Disease Control and Prevention

- Christen, "Charles C. Bass, M.D.," 9; Matas, *Dr. Charles C. Bass*, 6. Charles Edmund Simon (1866–1927) opened the first diagnostic laboratory in Baltimore (1897) and at Johns Hopkins, started the first known teaching program on filterable viruses (1922) and compiled a large collection of virus specimens. William Sydney Thayer (1864–1932) was a long-time faculty member of the Johns Hopkins University School of Medicine (from 1896 to 1921), which included terms as head of the hospital medical clinic and director of the Department of Medicine. At the medical school, Thayer was responsible for organizing the first course in clinical microscopy.
- Matas, *Dr. Charles C. Bass*, 10. Wright was an honorary member of AAI (1914–1920).
- Matas, *Dr. Charles C. Bass*, 7. See also George Dock and Charles C. Bass, *Hookworm Disease: Etiology, Pathology, Diagnosis, Prognosis, Prophylaxis, and Treatment* (St. Louis, MO: C. V. Mosby Company, 1910).
- Thomas Waisley, "Public Health Programs in Early Twentieth-Century Louisiana," *Louisiana History: The Journal of the Louisiana Historical Association* 41, no. 1 (2000): 42.
- Dock and Bass, *Hookworm Disease*, 44. In his field research, Bass made the discovery that hookworm larvae were unable to thrive in the high clay soils of southern Louisiana. Bass and others were able to establish the pathology of uncinariasis in children, which included stunted growth and mental developmental issues.
- The parasitic protozoans were identified in 1880; the means of transmission by *Anopheles* mosquito was described in 1899.
- C. C. Bass, "A New Conception of Immunity: Its Application to the Cultivation of Protozoa and Bacteria from the Blood and to Therapeutic Measures," *Journal of the American Medical Association* 57, no. 19 (1911): 1534–35; C. C. Bass and F. M. Johns, "The Cultivation of Malarial Plasmodia (*Plasmodium vivax* and *Plasmodium falciparum*) In Vitro," *Journal of Experimental Medicine* 16, no. 4 (1912): 567–79.

parasitology, which had eluded such titans as Theobald Smith (AAI '20), opened countless new avenues of malarial research.¹³ It led to Bass's own three-month collaboration in 1912 with Colonel William C. Gorgas at Ancon Hospital in the Panama Canal Zone, where the high incidence of the disease threatened the Canal project.¹⁴



Anopheles mosquito feeding
Centers for Disease Control and Prevention

While a principal investigator at Tulane, Bass pursued increasingly expansive research interests, including the diseases caused by vitamin deficiency (beriberi and pellagra), diphtheria, dysentery, typhoid fever,¹⁵ and periodontal disease.

In mid-1914, Bass somehow became aware of a paper delivered at a Pennsylvania State Dental Society meeting, tentatively concluding that amoebas found in the gums of patients with periodontitis may be responsible for the disease. Bass seized on these early findings and collaborated with a colleague at Tulane, Foster M. Johns, on a series of periodontitis studies, producing two journal articles and a book within one and one-half years. Bass and Johns tentatively concluded that *Endameba buccalis* was responsible for periodontitis. In their findings, they issued what proved to be an apt caveat: they were unable to re-isolate *E. buccalis* to satisfy Koch's postulates. Despite this limitation, they proposed a treatment using a hypodermic injection of emetin to kill the amoeba and cure periodontitis.¹⁶ The dental community initially had a positive reaction to Bass's research and treatments, but the positive reception did not last. The science that supported their conclusions was soon refuted in dental literature



Huey P. Long, c. 1935
Library of Congress, Prints and Photographs Division, Harris & Ewing

and at meetings, and within one year, the central role of amoebas in periodontitis and the emetin treatment were completely rejected by the scientific community. Bass must have been chastened by this setback, for he put aside dental research for nearly one quarter century. He would, however, return to it energetically after his retirement from Tulane.¹⁷

Cunning Administrator

In 1922, Bass was elected dean of the Tulane University School of Medicine, which remained the only accredited medical school in the state. Although he maintained his professorship, his energy was focused almost exclusively on the administration of the school. During his 18 years as dean, Bass oversaw the expansion and relocation of the medical school from its cramped Canal Street facility to the Hutchinson Memorial Building that houses the medical school and research facilities still today. One initiative, in particular, drew strong resistance from populist Governor Huey Long. At issue was a new Tulane clinical facility that almost doubled the school's presence and influence at Charity Hospital, a nearly 200-year-old public institution in New Orleans. Long, who was intent on founding a public medical school in Louisiana, opposed the

elite private medical school's expanded clinical facility and authority at the state's hospital. With appointments to the board of directors for Charity Hospital being within the governor's purview, the board had become highly politicized under Long. In 1930 and 1931, the Long-appointed superintendent rescinded and denied Bass's appointments to the hospital on political grounds. As the dispute grew public, Long used the conflict to advance the construction of the Louisiana State University School of Medicine in New Orleans. Bass, however, did not back down on his appointments. By 1932,

13. Matas, *Dr. Charles C. Bass*, 8.

14. Bass was the head of the Tulane University School of Tropical Medicine to the Tropics for the Study of Malaria Expedition, 1912–1922. William C. Gorgas (1854–1920) was the chief sanitary officer in the Panama Canal Zone from 1904 to 1914.

15. Bass discovered a new method for diagnosing typhoid fever and presented his findings at the American Congress of Internal Medicine in Chicago in 1920. Whereas the previous method for testing for typhoid fever took 12–24 hours, Bass's new method required only a blood test at the patient's bedside and took just 10 minutes. C. C. Bass, "American Heart Likely to Benefit by Prohibition." *The Atlanta Constitution*, February 25, 1920.

16. Emetin is derived from ipecacuanha and had been used since the early nineteenth century to treat amebic dysentery. Edward B. Vedder, "Origin and Present Status of the Emetin Treatment of Amebic Dysentery," *Journal of the American Medical Association* 62, no. 7 (1914): 501–6.

17. Christen, "Charles C. Bass, M.D.," 10–11.

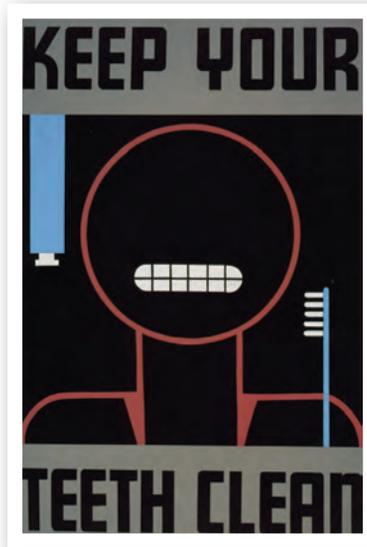
his appointees had received their privileges at Charity Hospital.¹⁸

Father of Preventative Dentistry

In 1940, as Bass turned 65, he reached the mandatory retirement age for Tulane. Although technically retired, he continued his research for the next 35 years. With the zeal of a crusader, he returned to the field of dental research. These were productive years for Bass, during which his research and successful clinical methodology ultimately earned him the moniker, “father of preventative dentistry.”¹⁹

In his seminal article, “The Cause and Prevention of the Loss of Teeth,” published in 1940, Bass asserted an “urgent need for an awaking of the situation” that tooth decay and loss should not be “considered to be necessary and unavoidable burdens of life.”²⁰ Rather, his research, using standard microbiological techniques, demonstrated that cavities and gum disease are caused by bacterial infections. Furthermore, he argued, these infections are preventable through proper dental hygiene.

Between the ages of 71 and 94, Bass published 32 journal articles, 26 of which were about dental hygiene. Many of these publications further elaborated on his “Right Kind” method for proper brushing and flossing techniques, including proper oral-care techniques for children and the elderly.²¹ He eventually designed a toothbrush and floss to work with his method that were so precise that their



Library of Congress, Prints and Photographs Division



Charles C. Bass
Images from the History of Medicine, National Library of Medicine

requirements included the exact thickness and shape of the bristle tips and number of turns per inch of a particular unwaxed nylon yarn.²² Bass’s articles also noted deficiencies in preventative dentistry in the military and in dental education. These articles fueled antipathies with the Public Health Service, American Dental Association, and the rest of organized dentistry and seldom appeared in dental journals.²³

Over a long scientific career, Charles C. Bass advanced public health. In his first chapter of scientific life, he pioneered hookworm disease etiology, pathology, and treatment. He also solved a confounding technical problem in malaria research by discovering how to cultivate the parasitic protozoa in vitro. In the second chapter of his career, as an administrator, he finessed the powerful Louisiana governor to expand the influence of the state’s only accredited medical school at the largest public hospital in New Orleans. In his final chapter, at a time when many of his colleagues had completely retired from the lab, he spearheaded public and professional awareness of the benefits of preventative dentistry, this time successfully defending his theory that “a clean tooth does not decay.”²⁴ In doing so, Bass secured rights to the epitaph he once suggested for himself: “He designed and promoted an effective method of personal hygiene.”²⁵ ■

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

Katlyn Burns, AAI History Intern, contributed to this article.

18. John Salvaggio, *New Orleans’ Charity Hospital: A Story of Physicians, Politics, and Poverty* (Baton Rouge, LA: Louisiana State University Press, 1992), 100–119; John Duffy, *The Tulane University Medical Center: One Hundred and Fifty Years of Medical Education* (Baton Rouge, LA: Louisiana State University Press, 1984), 146–52.

19. Christen, “Charles C. Bass, M.D.,” 16.

20. C. C. Bass, “The Cause and Prevention of the Loss of Teeth,” *New Orleans Medical and Surgical Journal* 93, no. 2 (1940): 229, 227.

21. The “Right Kind” method was first published in 1948.

22. Christen, “Charles C. Bass, M.D.,” 13.

23. *Ibid.*, 16.

24. Bass, “The Cause and Prevention of the Loss of Teeth,” 229.

25. Christen, “Charles C. Bass, M.D.,” 16.

For nearly 100 years, AAI members have been at the forefront of advancements in immunology and related disciplines. In this issue, we profile Elise Strang L'Esperance whose legacy included a number of firsts, both in her medical research and in the career distinction she achieved as a woman.

Elise Strang L'Esperance: Pioneer in Cancer Prevention and Recipient of Lasker Award

In 1916, **Elise L'Esperance, AAI 1920**,¹ became the first woman to be a lead author on an article published in *The Journal of Immunology (The JI)*.² Co-authored with her colleague at the Cornell University Medical College and editor-in-chief of *The JI*, Arthur Coca, AAI 1916, the article examined sources of error in the Wassermann reaction — the newly developed test for syphilis.³ This was not the last “first” to be credited to L'Esperance, for she was instrumental in breaking a number of barriers for women in medicine and changing the face of cancer prevention in the United States. For her ground-breaking work in cancer prevention, L'Esperance shared the 1951 Lasker Clinical Medical Research Award with cancer researcher Catherine Macfarlane. L'Esperance and Macfarlane were the first women to be awarded a Lasker for medical research.

Born in 1878, Elise was the youngest of three daughters of Albert Strang, a Yorktown, New York, physician, and Kate Depew Strang, sister of Chauncey Depew, a U.S. senator, lawyer to Cornelius Vanderbilt, and railroad president. Encouraged by her father to pursue a career in medicine, Elise enrolled in the Women's Medical College of the New York Infirmary for Indigent Women and Children (hereafter referred to as New York Infirmary),⁴ taking advantage of opportunities created by women's medical education pioneer Elizabeth Blackwell.⁵ While a student, Elise married David A. L'Esperance, a New York attorney, and received her medical degree as Elise L'Esperance, graduating in the college's final class in 1899.⁶

L'Esperance began her medical career as a clinician by interning at Babies Hospital in New York and then entering private practice as a pediatrician, first in Detroit and then in New York City. Frustrated that medicine was unable to spare her patients the ravages of diseases having no known cure, Elise sought to switch her emphasis to medical research. In 1908, she was appointed to the New York Tuberculosis Commission under the esteemed William H. Park, AAI 1916.⁷ As a result of her work with the commission, she became



Photo Credit: New York West Cornell Medical Center Archives

increasingly interested in the research opportunities afforded by a career in pathology. In 1910, she joined the staff of James Ewing, a cancer specialist in the Department of Pathology, Cornell University Medical College, becoming his first female research assistant.

Elise showed much promise and was promoted to instructor in 1912, awarded a research fellowship to study in Munich, Germany, in 1914, and, in 1920, was promoted to assistant professor — becoming the first woman to attain a professorial rank at the medical school.

During this same period, she also served as the director of laboratories of the New York Infirmary.⁸ After obtaining the rank of assistant professor, L'Esperance remained at Cornell for another 12 years of productive research and at the New York Infirmary for an additional 26.⁹

1. L'Esperance joined AAI when the New York Society for Serology and Hematology was dissolved in 1920. She was a member until she passed away in 1959.
2. In the early years of *The JI*, articles were often written by a single author. When an article was co-authored, the designated first author had directed the research, and the second author was a contributor. Ruth L. Stone, M.S., AAI 1922, was the first female author in *The JI* (as a second author).
3. Elise S. L'Esperance and Arthur F. Coca, "Further Experiences with the Isolated Organ Lipoids as 'Antigen' in the Wassermann Test," *The Journal of Immunology* 1, no. 2 (1916): 129–158.
4. The New York Infirmary for Indigent Women and Children was founded by Elizabeth Blackwell in 1857 to serve the poor of New York City and provide positions for women physicians and a training facility for female nursing students. Blackwell opened Women's Medical College in 1868 to teach and train female physicians. L'Esperance followed Blackwell's spirit at the New York Infirmary in creating clinics that were staffed entirely by women. The New York Infirmary merged with Beekman Downtown Hospital in 1981, and today is the New York Downtown Hospital.
5. Elizabeth Blackwell (1821–1910) earned a medical degree in 1849, becoming the first female to do so in the United States.
6. She graduated in 1899, but she contracted diphtheria and was unable to receive her degree until 1900.
7. William Hallock Park (1863–1939) was the director of the New York City Health Department Laboratory from its founding in 1893 until his retirement in 1936. He is best known for his work in applying bacteriological and immunological methods to public health in New York City, notably his successful clean milk and anti-diphtheria campaigns. Park was an AAI member from its founding until his death. He also served as president in 1918, as well as on the Advisory Board of *The JI* (1920–1936).
8. *The New York Times*, "Dr. L'Esperance Specialist, Dead," 22 January 1959: 31.
9. She later returned to Cornell University Medical College as professor of preventative medicine (1950–1959).

L'Esperance

In the early 1930s, L'Esperance's mother succumbed to cancer. Two years later, her cousin Chauncey Depew, Jr., passed away. Having died a bachelor, Depew left a large family inheritance to his cousins, who had already inherited large sums of money from their mother.¹⁰

In honor of their mother, L'Esperance and a sister used funds now available to them to create the Kate Depew Strang Clinic for Cancer and Allied Diseases at the New York Infirmary. With new equipment and its own staff endowed by the sisters for the first two years, the clinic was established as a separate department of the hospital. L'Esperance served as its first director, stating that the clinic's mission was to bring the use of modern techniques to the diagnosis and treatment of cancer in women. At its dedication, Ewing declared that the clinic represented "a pioneer step...devoted to the greatest problem in medicine and probably the greatest hazard in human life — cancer."¹¹ On its first anniversary celebration, First Lady Eleanor Roosevelt praised the sisters' "unselfish generosity."¹²

Shortly after founding the clinic, L'Esperance became convinced that the best way to prevent cancer from developing into malignant tumors lay in its early detection through use of the most modern techniques for physical examinations. The causes of cancer, after all, remained unknown. She would endeavor to enact her "tentative plan to prove whether prevention and early diagnosis" of cancer were effective. If so, she maintained that her approach "could become a practical part of a medical health service."¹³

Fortunately, L'Esperance had the education, training, and financial resources to act upon her convictions and do something that ultimately proved revolutionary. In May of 1937, she founded the Kate Depew Strang Cancer Prevention Clinic at the New York Infirmary. The goal of this new clinic was to identify early-stage cancers and pre-cancerous conditions because, according to L'Esperance,

FURTHER EXPERIENCES WITH THE ISOLATED ORGAN LIPOIDS AS "ANTIGEN" IN THE WASSERMANN TEST

ELISE S. L'ESPERANCE AND ARTHUR F. COCA

From the Departments of Pathology and Experimental Pathology in the Medical College of Cornell University, New York

Received for publication, November 1, 1915

Our previous publications (1) upon the Wassermann reaction have dealt chiefly with the technique of the test. We have called attention to two important sources of error that attach to the use of the isolated organ lipoids (Noguchi) as "antigen." These were: first, the non-specific or "pseudo-reaction" that is sometimes obtained with the originally prescribed quantity of "antigen" when the serum to be tested has not been heated; and secondly, the prezone phenomenon of wanting or weak reaction, which sometimes occurs with positively reacting sera where the larger quantities of the lipoid emulsion are used.

In a subsequent larger series of examinations we have not only confirmed those observations, but, through our association with Dr. E. L. Keyes and with the generous assistance of Dr. D. W. MacKenzie, Dr. B. S. Barringer and Dr. J. D. Kernan, Jr., we have been able, also, to reach a definite conclusion as to the relative clinical efficiency of our technical method in the diagnosis of syphilis.

The technique employed was not essentially changed from that described in our former publications. The serum to be examined was used undiluted in a quantity of 0.02 cc., or it was diluted 1 to 10 and the diluted serum was used in a quantity of 0.2 cc. The sera were examined usually in the unheated condition.

The guinea pig's serum was used in a 1 to 10 dilution in quantity of 0.1 cc.

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"effective treatment is that instituted at a time when the process is localized."¹⁴ The clinic was a first-of-its-kind in the United States in its provision of a "complete physical examination of women, with especial reference to cancer."¹⁵ The Cancer Prevention Clinic did not treat patients. Patients diagnosed with potential cancer were referred to their personal doctors.

10. *The New York Times*, "C. M. Depew JR. Left Estate of \$6,199,241" 17 November, 1931: 28. The article states that each cousin inherited \$1,931,810. Elise and her sisters also inherited money that their mother received upon the death of Chauncey Depew in 1928. See NYT, "Depew Will Give \$1,000,000 to Yale" 19 April 1928: 1. There is no clear evidence of which inheritance provided initial funding for the first clinic.

11. *The New York Times*, "New Cancer Clinic Opened by Women," 12 April 1933: 11.

12. *The New York Times*, "Clinic Praised by Mrs. Roosevelt," 27 April 1934: 11.

13. Elise S. L'Esperance, "The Early Diagnosis of Cancer," *Bulletin of the New York Academy of Medicine* 23, no. 4 (1947): 397. [Emphasis in original removed]

14. L'Esperance, 395. [Emphasis in original]

15. Catherine Macfarlane, "Cancer Prevention Clinics," *Journal of the American Medical Women's Association* 1, no. 1 (1946): 2.

The physical examination at the clinic typically included mouth, nose, throat, pelvic, and rectal examinations, urinalyses, blood tests, and a full-plate x-ray of the chest. L'Esperance remained vigilant in the addition of new techniques as they became available for early detection of the disease. These included a test for diabetes as well as a technique devised by George Papanicolaou to detect cervical cancer (today known as the Pap smear). The latter led to the enduring use of the Pap smear as part of a regular gynecological exam.

The mission of the Cancer Prevention Clinic included educating patients about the importance of routine physical examinations to identify cancer early. The clinic was also committed to alerting patients to what were deemed “predisposing factors” for cancer. Among these factors, L'Esperance included the “excessive use of tobacco and other chronic irritants.”¹⁶

The preventative clinic model L'Esperance created proved so successful in identifying early-stage cancers and pre-cancerous cells that Ewing asked her to create a similar institution at Cornell-affiliated Memorial Hospital. The first clinic opened to women in 1940 and was followed by a clinic for men in 1944. By 1947, when the newly constructed building of the Kate Depew Strang Cancer Prevention Clinic at Memorial Hospital Center was dedicated, cancer was the second-leading cause of death in the United States, as the death rate had continued

increasing unabated since the turn of the century.¹⁷ The idea of a cancer prevention clinic was revolutionary in 1932, but, by 1947, it was hailed as “the most powerful tool thus far devised” for the early detection of cancer.¹⁸

The preventative clinic model was copied quickly across the United States. Clinics opened in Philadelphia (1938) and Chicago (1943). By 1947, 181 clinics had opened in 30 states and in almost every major city across the country.¹⁹

In addition to the Lasker Award, L'Esperance received the Clement Cleveland Medal of the New York City Cancer Committee in 1942, becoming the first woman to do so. She also served as the first editor of the *Journal of the American Medical Women's Association*, as well as an associate commander of the Women's Field Army of the American Society for the Control of Cancer.²⁰

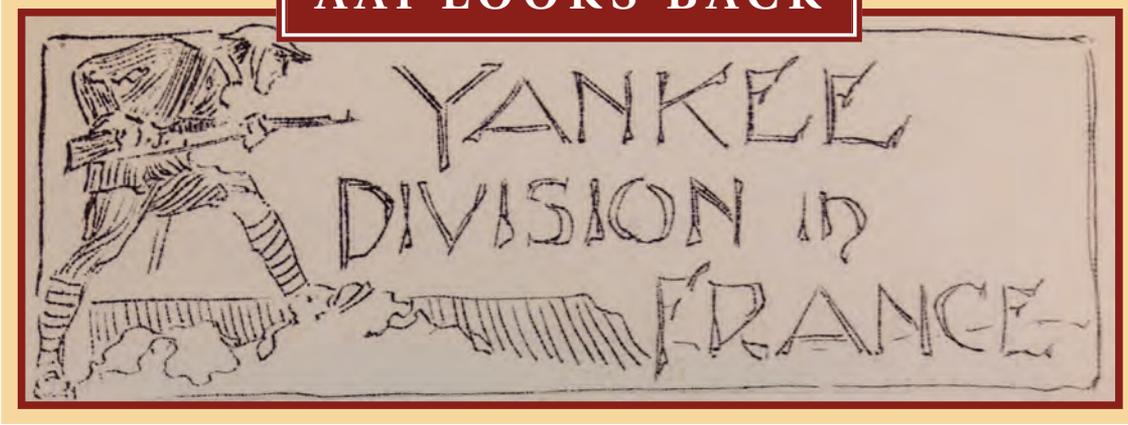
16. L'Esperance, 397–399.

17. The death rates for infectious and parasitic diseases, by contrast, were declining. With the exception of the pandemic influenza of 1918–1920, heart disease was the leading cause of death in the United States, U.S. Public Health Service, *Vital Statistics of the United States, 1947 Part I* (Washington, DC, Government Printing Office), 111; U.S. Department of Commerce, *Mortality Statistics, 1932* (Washington, DC, Government Printing Office), 14.

18. *The New York Times*, “Clinic Dedicated in Cancer Battle,” 13 November 1947: 20. Quotation from Austin V. Deibert, chief of the cancer control subdivision of the National Cancer Institute.

19. Macfarlane, 2; *The New York Times*, “181 Centers Push Fight on Cancer,” 24 November 1947: 25.

20. The American Society for the Control of Cancer adopted the name American Cancer Society in 1945. The Women's Field Army was responsible for major cancer education campaigns in the 1930s and 1940s.



Immunologists during the First World War: One Soldier-Scientist's Experience

Stanhope Bayne-Jones (AAI 1917, President 1930–31)

Byond its untold cost in human suffering, the First World War profoundly affected scientific and biomedical research both in Europe and the United States. Researchers on both sides of the Atlantic necessarily refocused their intellectual energies to work in support of their nations' war efforts. As armies clashed, communications among scientists in warring nations ceased, as did opportunities for U.S. medical students to study in Europe. However huge its impact on individual M.D.s' lives and on worldwide biomedical research, the war also served to hasten dramatic changes already underway in American medical education and scientific research.

Transatlantic ties

Advancements in American science and medicine in the late nineteenth century owed a great deal to Europe. Until at least the turn of the century, U.S. medical schools and research institutes were considered inferior to their European counterparts, especially those in Germany. Men and women of science were, therefore, expected to complete their education by studying at European universities or laboratories before returning to the United States. German universities alone attracted approximately 18,000 American students from 1870 to 1900.¹

This transatlantic migration began to decline in the first 15 years of the twentieth century as a full-scale university system began to develop in the United States. For university administrators, the new system was able to tap the cadre of scientists and physicians who had studied in

Germany. And university medical schools were compelled to standardize basic educational and clinical requirements after the *Flexner Report* of 1910 criticized the schools for their failure to produce graduates of consistent quality and abilities.² As higher education in the United States evolved, the transatlantic migration slowed significantly. At the outset of the war, it ceased almost entirely.

Along with educational improvements came advancements in scientific and medical research. New scholarly societies formed, including AAI, founded in 1913, around newly defined disciplines and began publishing peer-reviewed journals, such as *The Journal of Immunology*, first published in 1916. Funding of science and medicine also changed dramatically. The federal government strengthened its commitment to scientific innovation, increasing the budget for research agencies, such as the National Bureau of Standards and the Public Health and Marine Hospital Service, and opening the Walter Reed Hospital (1909), where patient care, teaching, and research were integrated. University science and medical departments also increased their financial support for research. And, perhaps most significant, American businesses and leading philanthropists invested in science and medicine. The years 1900–1915 saw the establishment of the General Electric Research Laboratory (1900), the Rockefeller Institute of Medical Research (1901), the Carnegie Institution of Washington (1902), and the Rockefeller Foundation (1913).³

¹ Hugh Hawkins, "Transatlantic Discipleship: Two American Biologists and Their German Mentor," *Isis* 71, no. 2 (1980): 197–98.

² Abraham Flexner, *Medical Education in the United States and Canada: A Report to the Carnegie Foundation for the Advancement of Teaching, Bulletin Number Four* (New York: Carnegie Foundation, 1910); John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (New York: Penguin, 2005), 82–87. The Flexner Report brought national attention and scrutiny to the fact that few standards for admission and graduation existed for American medical schools. Shortly after the release of the report, medical schools were forced to raise their standards. Graduates of those schools that failed to conform to the new American Medical Association rating system motivated by the Flexner Report were denied medical licenses.

³ Daniel J. Kevles, "George Ellery Hale, the First World War, and the Advancement of Science in America," *Isis* 59, no. 4 (1968): 427–28.



Walter Reed General Hospital, ca. 1915
Library of Congress, Prints & Photographs Division,
Harris & Ewing Collection

One soldier-scientist's story

At the war's outset in Europe in August 1914, more than two and a half years before the U.S. Congress declared war on Germany on April 6, 1917, just 776 of the approximately 140,000 practicing physicians and M.D.s entering the new research facilities in the United States were serving in the military.⁴ By the end of February 1918, more than 15,000 doctors were serving, and, by the time of the armistice, nine months later, that number had grown to 38,000.⁵ During this period of rapid mobilization, the professional trajectories of thousands of American physicians were altered. Entering medicine at a time that the emergence of research laboratories in the United States widened the range of career choices, this generation of American M.D.s faced a new set of choices for service in wartime: they could serve as combat physicians, work in U.S. Army laboratories, or remain in their laboratories carrying out research necessary for the war effort.

One young M.D., who put his prestigious position in immunology research on hold and volunteered in May 1917 for early deployment as a combat physician, was Stanhope Bayne-Jones, a future AAI president.

Continued next page

Stanhope Bayne-Jones

The 17th President of AAI

A Biographical Sketch

Born in New Orleans on November 6, 1888, Stanhope Bayne-Jones was orphaned when his father committed suicide in 1894, one year after his mother had passed away due to complications arising from the birth of his younger brother. Bayne-Jones lived with his grandfather, Joseph Jones, a practicing physician and a professor of medicine and chemistry at Tulane University, for two years, until Joseph's death in 1896.

After a childhood filled with boarding schools and moves from one relative's home to another's, Bayne-Jones entered Yale, where he received his A.B. in 1910. Determined to follow in his grandfather's footsteps, he began his medical studies at Tulane University before transferring to the Johns Hopkins University in 1911. He received his M.D. in 1914 and remained at the Johns Hopkins Hospital as house officer (1914–15) and assistant resident pathologist (1915–16). After he was appointed head of the new Laboratory of Bacteriology and Immunology at Johns Hopkins in early 1916, Bayne-Jones studied bacteriology and immunology under Hans Zinsser (AAI 1917, president 1919–20) at the Columbia University College of Physicians and Surgeons in New York for six months before the laboratory opened.

Bayne-Jones joined the U.S. Army Medical Reserve Corps (MRC) in 1915. He was commissioned at the rank of first lieutenant and promoted to captain the following year. In May 1917, he volunteered to be integrated into the British Expeditionary Force. He was reassigned to the American Expeditionary Forces upon their arrival in March 1918. After the armistice, he was promoted to major and remained in Germany until he was relieved of active duty in May 1919.

Bayne-Jones returned to Johns Hopkins in the summer of 1919 and became assistant professor of bacteriology the following year. In 1923, he accepted a position as a professor of bacteriology at the recently opened University of Rochester School of Medicine and Dentistry. He left Rochester in 1932 and became a professor of bacteriology at Yale University School of Medicine, where he was appointed dean three years later. From 1932 to 1938, he was also Master of Trumbull College at Yale.

When the Second World War began in 1939, Bayne-Jones was promoted to lieutenant colonel in the MRC and, two years later, headed the Commission on Epidemiological Survey of the Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army. From 1942 to 1946, Bayne-Jones was once again an active-duty officer, serving multiple positions within the Office of the Surgeon General. He quickly rose through the ranks, becoming colonel in 1942 and brigadier general in 1944. He was relieved from active duty in 1946 and, the following year, accepted an appointment as president of the Joint Administrative Board of the New York Hospital-Cornell Medical Center, a position he held until 1953. After serving as the technical director of research and development for the Office of the Surgeon General (1953–56), Bayne-Jones was appointed by the secretary of the U.S. Department of Health, Education, and Welfare in 1957 to chair an advisory committee charged with establishing guidelines for National Institutes of Health research following that year's dramatic increase in the NIH budget.

His many military and civilian honors include a British Military Cross (1917), a French Croix de Guerre (1918), election to the American Philosophical Society (1944), the U.S. Typhus Commission Medal (1945), the Chapin Medal of the Rhode Island State Medical Society (1947), the Bruce Medal of the American College of Physicians (1949), the Passano Foundation Award (1959), and a Decoration for Outstanding Civilian Service from the U.S. Army (1965).

In addition to serving AAI as president (1930–31), Bayne-Jones was an associate editor of *The Journal of Immunology* (1936–49).

Bayne-Jones died at his home in Washington, DC, on February 20, 1970, at the age of 81.



Stanhope Bayne-Jones, ca. 1917
National Library of Medicine, Stanhope
Bayne-Jones Papers

⁴ Barry, *The Great Influenza*, 139.

⁵ Dorothy A. Pettit and Janice Bailie, *A Cruel Wind: Pandemic Flu in America, 1918–1920* (Murfreesboro, TN: Timberlane, 2008), 43; Barry, *The Great Influenza*, 139–40.

This biographical sketch is compiled from Stanhope Bayne-Jones, "Curriculum Vitae," American Association of Immunologists Records, Box 8, Folder 11, University of Maryland, Baltimore County, and Albert E. Cowdrey, *War and Healing: Stanhope Bayne-Jones and the Maturing of American Medicine* (Baton Rouge: Louisiana State University Press, 1992).

His experiences illustrate some of the many challenges and issues faced by physicians, including future immunologists, in military service. All would face such dilemmas as when and where to volunteer their services, how to cope with the trauma of war, and how to readjust to the laboratory after the war.

Stanhope Bayne-Jones earned his M.D. at the Johns Hopkins University in 1914 under William Welch, dean of the Johns Hopkins School of Medicine.⁶ Founded in 1893 and based on the German system, the Johns Hopkins University School of Medicine was praised in the Flexner Report as “the first medical school in America of genuine university type.”⁷ After graduating with high honors, Bayne-Jones remained at Johns Hopkins, where he rose from House Officer in Medicine to Assistant Resident Pathologist within one year. In early 1916, he was offered and accepted the opportunity to head the new Laboratory of Bacteriology and Immunology in the Department of Pathology at the Johns Hopkins Hospital.

Despite research opportunities emerging in the rapidly changing American medical and scientific landscape, the U.S. declaration of war in April meant that recent graduates, by May 1917, were considering how they could best contribute to the war effort.

Enlisting qualified army physicians in the Medical Reserve Corps (MRC)

The number of army physicians rose dramatically with the rapid growth of the standing U.S. Army following the 1917 draft. The ranks of the army had expanded from fewer than 200 thousand troops in March 1917 to over one million within a matter of months. Many of the most prominent men in medicine volunteered their services, including Welch, Victor Vaughan⁸ (AAI 1915), and Simon Flexner⁹ (AAI 1920).

Already, at the outset of hostilities in Europe, U.S. Surgeon General William C. Gorgas was concerned with enlisting enough qualified physicians in the Army MRC to ensure military preparedness. One of the first physicians he solicited was his grandnephew Stanhope Bayne-Jones. When “Uncle Willie”¹⁰ wrote his nephew in the summer of 1915, Bayne-Jones was just beginning his career at Johns Hopkins.¹¹



The Johns Hopkins Hospital, ca. 1910

Library of Congress, Prints & Photographs Division, Detroit Publishing Company Collection

Gorgas described the role that the MRC would play if the United States were to enter the war and the duties of corps volunteers as follows:

*Under the law you could never be called into service, except with your own consent; nor is it compulsory to have any military training. In case of war, if you should desire field service, military training that you had received before would be a very great advantage to you, but the large bulk of the Reserve Corps would not go into the field in case of war. Unless you desire field service you would be placed on duty, in case of war, at some general hospital where your duties would be purely professional. In the time of war we would have general hospitals located in most of our large cities. The great object of the Reserve Corps is to get a registered list of medical men who could be called upon for such duties, always with their own consent.*¹²

Bayne-Jones needed little encouragement. He enlisted almost immediately and was commissioned as a first lieutenant in the U.S. Army MRC on August 18, 1915.¹³

⁶ William Welch (1850–1934), physician, scientist, and administrator, served as dean of Johns Hopkins School of Medicine and was the first director of the School of Hygiene and Public Health as well as the Institute of the History of Medicine. Although never an AAI member, Welch served on the Advisory Board of *The Journal of Immunology* (1916–34). In 1896, Welch founded *The Journal of Experimental Medicine*. For more information on the relationship between Bayne-Jones and Welch, see Albert E. Cowdrey, *War and Healing: Stanhope Bayne-Jones and the Maturing of American Medicine* (Baton Rouge: Louisiana State University Press, 1992), especially chapters 2 and 3.

⁷ Flexner, *Medical Education*, 12.

⁸ Victor Vaughan (1851–1929), biochemist, hygienist, public health authority, medical educator, and dean of the University of Michigan Medical School (1891–1920), served on the Advisory Board of *The Journal of Immunology* (1916–1929).

⁹ Simon Flexner (1863–1943), scientist and first director of the Rockefeller Institute for Medical Research (1901–1935), was an Active (1920–1936) and Honorary (1936–1943) member of AAI and served on the Advisory Board of *The Journal of Immunology* (1916–1935).

¹⁰ Gorgas's mother was the great aunt of Bayne-Jones.

¹¹ William Gorgas to Stanhope Bayne-Jones (SBJ), June 17, 1915, Stanhope Bayne-Jones Papers, Box 7, Folder 16, “Medical Reserve Corps, 1915–1916,” National Library of Medicine, Bethesda, MD [hereafter “SBJP-NLM”].

¹² William Gorgas to SBJ, June 29, 1915, SBJP-NLM, Box 7, Folder 16, “Medical Reserve Corps, 1915–1916.”

¹³ Memo from the Adjutant General of the Army to SBJ, August 18, 1915, SBJP-NLM, Box 7, Folder 16, “Medical Reserve Corps, 1915–1916.”

On April 6, 1917, the same day that the U.S. Congress issued its formal declaration of war, the AAI Council interrupted its proceedings to pass a resolution offering “the services of trained bacteriologists and immunologists and the facilities of their respective laboratories” to federal and state governments.¹⁴

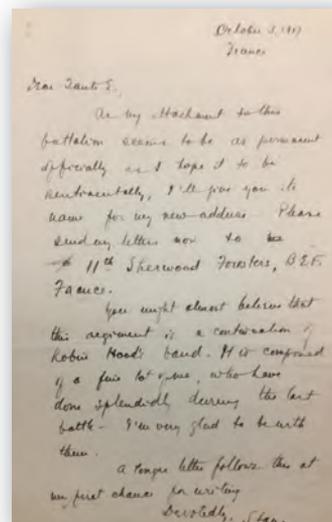
Many members remained in their laboratories during the war, pursuing research for the war effort. The majority of this research, typified by the work of Anna Wessel Williams (AAI 1918) and William H. Park (AAI 1919, president, 1918–19), was focused on the influenza pandemic (see *AAI Newsletter*, March/April 2012). Convinced that scientists at the Rockefeller Institute could better support the war effort if they remained together than if they were dispersed, Simon Flexner arranged with Gorgas to keep the Rockefeller laboratories intact as one army unit.¹⁵ Other AAI members serving in the MRC were sent to U.S. Army training camps or military hospitals and laboratories in Europe. Among the volunteers were Richard Weil (AAI 1914, president 1916–17), who served as chief of medical service at Camp Wheeler, Georgia, until November 1917, when he died of complications from pneumonia; Martin J. Synnott (AAI 1913, secretary 1913–18), who studied the pandemic influenza at Camp Dix, New Jersey;¹⁶ Rufus Cole (AAI 1917, president 1920–21), who chaired the Pneumonia Commission in charge of researching outbreaks of the disease at Army training

camps;¹⁷ and Hans Zinsser (AAI 1917, president 1919–20), a good friend of Bayne-Jones, who was stationed in France as an Army sanitary inspector and assistant director of the Division of Laboratories and Infectious Diseases.¹⁸

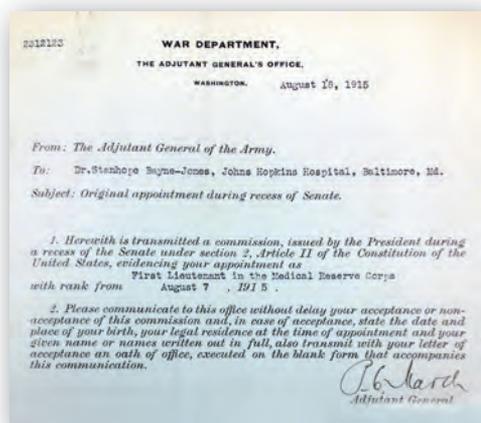
Preparing for the front

The vast majority of American troops spent 1917 training in the United States and did not arrive in Europe until spring 1918. Bayne-Jones, however, was one of a relatively small number of American soldiers who volunteered to be integrated into the British Expeditionary Force (BEF) nearly one year before the American Expeditionary Forces arrived *en masse*. Assured that his position at Johns Hopkins would be waiting for him upon his return, Bayne-Jones set sail for London on the S.S. *Orduna* in May 1917 and joined the 69th Field Ambulance of the BEF by the end of the month.¹⁹ Shortly after arriving in France with the 69th Field Ambulance, he explained his decision to volunteer in a letter home to his sister Marian: “With these big things going on I could not stay still in Baltimore with the prospects of remaining repressed as a Teacher of Bacteriology or of being assigned to the prosaic medical duties of a Training Camp. No doubt both of these activities would be as useful and safer than what I can do over here; but this has the interest: It is like living in the Sunday pictorial of the New York Times.”²⁰

Stationed at a hospital behind the lines in May and early June, Bayne-Jones heard “wonder-tales” from the wounded British troops about an “earthquake battle,” which made him long to get to the front lines. By the end of the month, he had received orders sending him to the Belgian front. After receiving mandatory training on the proper use of his gas mask, he boarded a train on June



Letter home, ca. 1917
National Library of Medicine, Stanhope Bayne-Jones Papers



Bayne-Jones MRC commission, ca. 1915
National Library of Medicine, Stanhope Bayne-Jones Papers

¹⁴ “Minutes of the Fourth Annual Meeting—1917,” April 6–7, 1917, AAI Archives.

¹⁵ Barry, *The Great Influenza*, 140.

¹⁶ Martin J. Synnott and Elbert Clark, “The Influenza Epidemic at Camp Dix, N.J.,” *The Journal of the American Medical Association* 71, no 22 (1918): 1816–21.

¹⁷ Other members of the Pneumonia Commission included many future AAI members and presidents: Francis Blake (1921, president 1934–35), Thomas Rivers (1921, president 1933–34), and Eugene Opie (1923, president 1928–29). Pettit and Baillie, *A Cruel Wind*, 81–82; Barry, *The Great Influenza*, 164–65.

¹⁸ Simeon Burt Wobach, “Hans Zinsser, 1878–1940,” *Biographical Memoirs* (Washington, DC: National Academy of Sciences, 1947), 327–28.

¹⁹ W. MacCallum to SBJ, May 1, 1917, SBJP-NLM, Box 7, Folder 12, “Johns Hopkins University, 1915–1918”; Stanhope Bayne-Jones, “Curriculum Vitae (to 1968),” American Association of Immunologists Records, Box 8, Folder 11, “Bayne-Jones, Stanhope,” Center for Biological Sciences Archives, University of Maryland, Baltimore County [hereafter AAI-UMBC]. Bayne-Jones was initially assigned to the 23rd Division, 69th Field Ambulance, BEF.

²⁰ SBJ to Marian Jones, June 11, 1917, SBJP-NLM, Box 7, “Correspondence.”

20, 1917, to join his unit near Ypres. As the nearly 24-hour train ride to the front came to an end, he recorded his initial impressions of the war: "We not only hear the guns, but sometimes see the effects of their shells, which are still far enough away to be 'interesting.'"²¹

The work that Bayne-Jones did in the 69th was a far cry from the research he left in Baltimore. He served in many capacities as a part of the field ambulance, the most basic unit of medical care in the BEF. Every division had three field ambulance units, each with two companies of stretcher bearers and orderlies. When soldiers were injured, they were taken from the front by stretcher to an assembly point on the line in the rear, where they were triaged. If their wounds were serious enough, they were sent further behind the lines to a central station, then to a divisional collection point, and, finally, to an advanced dressing station. At each point, the wounded soldier was assessed, and if he was deemed to be in too poor a condition, he was treated on the spot rather than sent to the next station.²²



American soldiers in the trenches, ca. 1918
National Library of Medicine, Stanhope Bayne-Jones Papers

In the trenches

Bayne-Jones slowly worked his way to the front lines. Under mortar fire for the first time in early July, he reported that he was not as "scared as I thought I would be."²³ By month's end, however, the reality of the war began to set in after a night of shelling and gas attacks by the Germans.

Nearly every night [the German army] sends thousands of shells of poison gas which complicate life very much. We have to sit up long hours with our heads in the gas helmets, sweating, half suffocated, dribbling, hardly able to see through the eye pieces that get so steaming it makes it hard to take care of the wounded, and the poor fools who lose their heads and get gassed because they forget to put on their helmets. . . . I believe I'd rather get bumped by a shell than spend nights down in one of those narrow saps, which have been inhabited by men and populated by vermin the last three years.²⁴

Despite his first taste of the horrors of war, Bayne-Jones was steadfast in his desire to remain in the field hospital. He found that the "work to be done here was as useful as any that I could accomplish by sticking at the Base. . . . [I]t certainly is more rewarding to take care of the men when they are in the most trouble. Even without that, the sights and thrilling parts we sometimes share make the seats on the stage worth the price of the risk."²⁵

Reflecting on his initial encounter with trench warfare, Bayne-Jones wrote that it was "my first dash of real life." He confessed, however, that the "medical experience is nil." "I've seen a lot of ghastly wounds and blood of course," he explained, "but we handle cases only to get them back to the hospital, and hence cannot follow them for study. Besides I seem to have lost interest in medicine and bugs—temporarily." He still intended to "settle down as a 'professor' somewhere" after the war.²⁶ But, as he admitted three months later in a letter home, he was forgetting "everything I ever knew of Bacteriology and medicine." Yet he had no regrets: "I'll be pretty ignorant of what I was trained to follow when this war is over, but I have seen some things! And shared the mud and cold with men 'out there'—and that will give me much consolation until I learn the other once more."²⁷



Bayne-Jones (front row, center) on the front, ca. 1918
National Library of Medicine, Stanhope Bayne-Jones Papers

²¹ SBJ to Edith Bayne Denegre ("Tante E."), June 23, 1917, SBJP-NLM, Box 7, "Correspondence."

²² Cowdrey, *War and Healing*, 55.

²³ SBJ to Tante E., July 4, 1917, SBJP-NLM, Box 7, "Correspondence."

²⁴ SBJ to Marian Jones, July 21, 1917, SBJP-NLM, Box 7, "Correspondence."

²⁵ SBJ to Tante E., August 5, 1917, SBJP-NLM, Box 7, "Correspondence."

²⁶ SBJ to Marian Jones, August 12, 1917, SBJP-NLM, Box 7, "Correspondence."

²⁷ SBJ to Tante E., October 27, 1917, SBJP-NLM, Box 7, "Correspondence."

Life on the front, with its “quick mud and chilly rain, and the immeasurable suffering,” as well as constant shelling, became almost a regular routine for Bayne-Jones in late 1917 and early 1918.²⁸ Early in the new year, a holiday care package from home finally arrived. The welcomed contents included “shaving soap, fine glycerin soap, some poison soap for the ‘totos’ as the poilus²⁹ call lice, cold cream, Vaseline, and a big lot of Hershey’s Chocolate.”³⁰ Lice and threadbare uniforms had been recurring themes of his stories home.

The Americans arrive

When the American Expeditionary Forces arrived in Europe in spring 1918, Bayne-Jones knew that he would soon be reassigned to an American unit, and he acknowledged that there were times he wished he “were back with the interests of the Laboratory.”³¹ In March, he was relieved from duty with the English battalion and ordered to report to a U.S. Army research laboratory in Paris, far removed from the “show” at the front.³² Although he “couldn’t have asked for better opportunities than were offered” at the laboratory, Bayne-Jones “felt that I *couldn’t* stick at a desk back there, while there was a war going on up front.”³³ A position as a battalion doctor was “by far and away the best for me as a human being, even if I am forgetting all the technical training I ever had, and which I believe is the best my efforts can do for the men over here.”³⁴ His request for a transfer from the laboratory was granted, and he soon returned to the front in eastern France as the battalion surgeon to the 26th Division, 3rd Battalion, 101st Infantry.³⁵

As many of the newly won trenches on the French front were similar to his first experience with the British—knee deep in mud and infested with rats and lice—Bayne-Jones taught elementary sanitation to the new troops.



German trench, ca. 1918

National Library of Medicine, Stanhope Bayne-Jones Papers

His role as battalion surgeon extended beyond the men under his watch to a “civilian’ practice in some poor villages” that his battalion had liberated from the Germans. It was a role that gave Bayne-Jones some comfort and relief, as “most of my patients were kids five or seven years old, with various troubles. All of them look like the lovely pictures in those old French song books we used to have and are appealing bright little people. It is very pleasant to be able to do anything for them.”³⁶

The 101st saw constant action throughout the majority of the spring of 1918, and a certain mix of weariness and wonderment had replaced Bayne-Jones’s initial excitement in his letters home.

*My luck has been with me this time—I have just gotten out of places before shelling began, or come into a sector just after the shelling has ended. Last night, however, a German aeroplane stopped over us in the twilight and gave us quite a scare with his machine gun. When you realize that the bullets are going beyond you, the exhibition seems lovely. The bullets sound like picking the three top strings of a harp, and the tracer-bullets on fire look like fireflies in the evening.*³⁷

A newfound concern for his own mortality also began to appear in his letters. “You never know when the noise and iron are going to drive your spirits out to the quiet fields above the balloons and aeroplanes,” he wrote in May.³⁸ Bayne-Jones admitted that the shells were getting on “my nerve now as they never did before”—the war was simply “going on too long.”³⁹

His letters also revealed a mounting homesickness. He described a “quiet moment” after going “over the top” on a successful raid, during which he “howled for the moon like a dog howling for the moon.”⁴⁰

²⁸ SBJ to Alma Denegre, October 18, 1917, SBJP-NLM, Box 7, “Correspondence.”

²⁹ Poilus was a warm, informal term for a French infantryman during the First World War, meaning, literally, hairy one.

³⁰ SBJ to Tante E., January 7, 1918, SBJP-NLM, Box 7, “Correspondence.”

³¹ SBJ to Tante E., December 12, 1917, SBJP-NLM, Box 7, “Correspondence.”

³² SBJ to George Denegre, December 23, 1917, SBJP-NLM, Box 7, “Correspondence.”

³³ SBJ to Tante E., April 5, 1918, SBJP-NLM, Box 7, “Correspondence” [emphasis in original].

³⁴ SBJ to George Denegre, June 20, 1918, SBJP-NLM, Box 7, “Correspondence.”

³⁵ For additional information on the U.S. Army ambulance service in the First World War, see Cowdrey, *War and Healing*, 62–63; Richard V. N. Ginn, *The History of the U.S. Army Medical Service Corps* (Washington, DC: Office of the Surgeon General and Center of Military History, United States Army, 1997), 37–51; Stanhope Bayne-Jones “The Duties of a Battalion and Regimental Surgeon,” November 25, 1918, SBJP-NLM, Box 9, Folder 11, “26th Yankee Division AEF—Armistice and After.”

³⁶ SBJ to Tante E., July 2, 1918, SBJP-NLM, Box 7, “Correspondence.”

³⁷ SBJ to Tante E., May 15, 1918, SBJP-NLM, Box 7, “Correspondence.”

³⁸ SBJ to Tante E., May 30, 1918, SBJP-NLM, Box 7, “Correspondence.”

³⁹ SBJ to George Denegre, June 20, 1918, SBJP-NLM, Box 7, “Correspondence.”

⁴⁰ SBJ to Marian Jones, June 2, 1918, SBJP-NLM, Box 7, “Correspondence.”

Pandemic influenza

In July, Bayne-Jones was promoted to regimental surgeon of the 103rd Infantry and given his first leave from the front after many months of tough fighting. He spent the majority of his time in Paris, where he contracted the pandemic influenza that was infecting and killing millions around the world. He described his bout with the “grippe” as taking “away interest in life” and explained that “the days have been so monotonous that I hardly noticed how many passed.”⁴¹ Aware that “influenza and pneumonia [have] hit some places” in America “pretty hard,” he worried about family at home “catching the ‘flu.’”⁴² His illness and convalescence kept Bayne-Jones from the front lines until September 1918.

Armistice and after

His return to the front coincided with the 47-day Meuse-Argonne Offensive,⁴³ part of the final offensive of the Allied forces. The conditions where the 103rd was located were “wet and cold,” and the men “slept in an oozing hole in the hillside.”⁴⁴ Beyond the physical effects of the war, Bayne-Jones was noticing mental changes in himself and his men.



Flu ward, ca. 1918

Library of Congress, Prints & Photographs Division

⁴¹ SBJ to George Denegre, September 2, 1918, SBJP-NLM, Box 7, “Correspondence.”

⁴² SBJ to Tante E., November 26, 1918, SBJP-NLM, Box 7, “Correspondence.”

⁴³ Also called the Battle of the Argonne Forest.

⁴⁴ SBJ to Susan Jones, September 27, 1918, SBJP-NLM, Box 7, “Correspondence.”

⁴⁵ SBJ to Susan Jones, September 27, 1918, SBJP-NLM, Box 7, “Correspondence.”

⁴⁶ SBJ to Marian Jones, November 11, 1918, SBJP-NLM, Box 7, “Correspondence.”

⁴⁷ SBJ to Marian Jones, January 16, 1919, SBJP-NLM, Box 7, “Correspondence.”

⁴⁸ Cowdrey, *War and Healing*, 69–71; Bayne-Jones, “Curriculum Vitae,” AAI-UMBC, Box 8, Folder 11, “Bayne-Jones, Stanhope.”

While the shells shriek overhead and burst with a deafening roar, throwing up clods of earth and chunks of the flotsam and jetsam of the battlefields, while the sizzling shrapnel rattles on the tin hats of the stalwart Yanks, crowding the muddy shell holes, while the machine gun bullets chirp overhead and spurt against the elephant iron, while all these horrors are taking place I am neither deafened nor afraid because I am in a hole 30 feet underground in a [German] dug-out. Isn't it a joke what the newspapers write up about battles!

Capt. Stanhope Bayne-Jones
November 5, 1918
France

“Like most unpleasant things, the war is in danger of being forgotten by us here at any moment—‘submerged into the unconscious processes,’ as the psychologists say.”⁴⁵

During the offensive, Kaiser Wilhelm II began making overtures that Germany would accept a peace treaty. And, at the stroke of 11:00 in the morning on November 11, 1918, “suddenly all the guns behind us stopped barking and rolling, the last ‘Freight car’ rattled over our heads, and all the machine guns suddenly stopped, though they had been rioting away up to the very last minute.” The quiet was “mysterious, queer, unbelievable,” but no one “shouted or threw his hat in the air.” Although the war was over, the soldiers of neither side found the armistice “exciting” at first. As the day turned into night, however, the front began to look to Bayne-Jones like “a Fourth of July celebration,” as unused flares and signal rockets from both armies illuminated the sky with their many colors well into the night.⁴⁶

On November 14, Bayne-Jones was promoted to the rank of major and became the sanitation inspector in Koblenz, Germany, as part of the army of occupation. Longing for home, he quickly turned to the same connections that got him to the front in the summer of 1917.⁴⁷ William Gorgas and William Welch were successful in their lobbying efforts, and Bayne-Jones was back on American soil on May 28, 1919. Two days later, he was honorably discharged from the U.S. Army.⁴⁸

Returning to the laboratory

Bayne-Jones soon returned to his academic position at Johns Hopkins to resume his research, but he found the transition back to life in the laboratory difficult. “Everybody here is either played out from having had to

work shorthanded in the school during the war or restless because they were in Europe during the war. Even the men who were in the Hopkins unit in France and have been back here since February are not yet settled into their work—or their feelings.”⁴⁹



Hans Zinsser
National Library of Medicine, History of Medicine Division

Hans Zinsser, who had served as a medical officer in France during the war, echoed his good friend’s sentiments about returning to the laboratory. In an early July 1919 letter to Bayne-Jones, he wrote, “It was difficult for me to readjust and the enthusiasm for the old problems is only now returning.”⁵⁰

Although the transition to civilian life may have been initially difficult for many immunologists, a number of them began making significant advancements

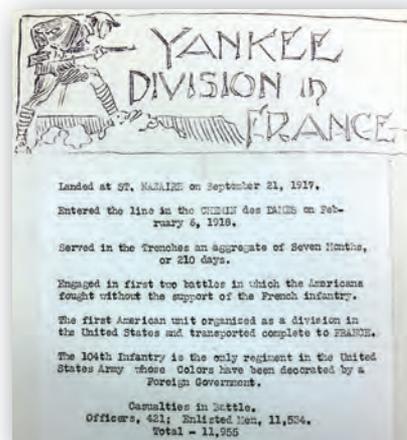
in clinical and basic research. The leadership skills that this generation of investigators had acquired during wartime service appear to have served them well in their rise through the ranks of academia and scientific and medical organizations, including AAI. Not only did Bayne-Jones and Zinsser become AAI presidents, so too did other veterans: Francis Blake (1921, president 1934–35), Thomas Rivers (1921, president 1933–34), and Eugene Opie (1923, president 1928–29).

For researchers in Europe, the war’s impact on their home institutions was more immediate and often longer lasting. Nobel laureate Jules Bordet (AAI 1960) was unable to continue his experimental research in occupied Belgium, although he did use the war years to write a classic book on immunity and infectious disease, *Traité de l’Immunité dans les Maladies Infectieuses*.⁵¹ Karl Landsteiner (AAI 1922, president 1927–28), then the chief pathologist at the Wilhelmina Hospital in Vienna, felt the war’s effects long after its conclusion. The shortage of resources in post-war Vienna forced him to leave his homeland for the Netherlands before permanently relocating to New York and joining the Rockefeller Institute in 1923.⁵²

Nevertheless, some of the war’s dislocations helped advance scientific research. Almroth Wright and Alexander Fleming of St. Mary’s Hospital, London, spent the war years serving in the Royal Army Medical Corps in a makeshift laboratory in France. It was Fleming’s first-hand

observations of the harmful effects of antiseptics on wounded soldiers that started him on the search for a non-toxic antibacterial substance that ended with his discovery of penicillin.⁵³

Although many immunologists, like Stanhope Bayne-Jones, survived the war and thrived in the decades that followed, there is no telling how many current and future immunologists were among the 9–10 million soldiers who died during the Great War or were included in the approximately 675,000 Americans, or the conservatively estimated 20 million worldwide, who fell victim to the pandemic influenza that the movement of troops helped create.⁵⁴



Yankee Division in France, ca. 1919
National Library of Medicine, Stanhope Bayne-Jones Papers



The Johns Hopkins Pathology Department Staff, ca. 1921.
(*Bayne-Jones, front row, second from left*)

National Library of Medicine, Stanhope Bayne-Jones Papers

⁴⁹ SBJ to Marian Jones, August 2, 1919, SBJP-NLM, Box 11, Folder 6, “Johns Hopkins University Correspondence I, 1919–1923.”

⁵⁰ Hans Zinsser to SBJ, July 8, 1919, SBJP-NLM, Box 11, Folder 5, “Johns Hopkins University Correspondence I, 1919–1923.”

⁵¹ Jules Bordet, *Traité de l’Immunité dans les Maladies Infectieuses* [Treatise on Immunity in Infectious Diseases] (Paris: Masson et cie, 1920).

⁵² Michael Heidelberger, “Karl Landsteiner, 1868–1943.” *Biographical Memoirs* (Washington, DC, National Academy of Sciences, 1969), 180.

⁵³ Leonard Colebrook, “Alexander Fleming. 1881–1955,” *Biographical Memoirs of Fellows of the Royal Society* 2 (November 1956): 117–27.

⁵⁴ Barry, *The Great Influenza*, 396–97.

The 1918–1919 Influenza Pandemic as Covered in *The Journal of Immunology* from 1919 to 1921

The deadly 1918–1919 influenza pandemic generated an impressive body of immunological research into the cause and prevention of the disease, and that urgency is reflected in the many articles on influenza published in *The Journal of Immunology* from 1919 to 1921. Because bacteria had been shown to be causative of other infectious diseases, including typhoid fever and diphtheria, and viruses were not yet understood as more than filter-passing agents, most scientists of the time believed the cause of influenza to be bacterial. German physician Richard Pfeiffer had isolated bacteria from influenza patients during the previous pandemic of 1892 and believed that these bacteria were the cause of influenza; the bacteria had come to be known as Pfeiffer's bacillus or *Bacillus influenzae* or *B. influenzae* (now *Haemophilus influenzae*). By the time of the 1918 pandemic, many scientists had embraced Pfeiffer's hypothesis, and researchers were attempting to establish the etiological significance of *B. influenzae* to the disease by examining cases from the unfolding influenza pandemic.

Immunologists cultured and isolated bacteria from patient samples, including throat swabs, sputum samples, pleural effusions, and lung exudates, with mixed results. In 1919, C. Roos from the Mulford Biological Laboratories in Glenolden, Pa., reported that a collective review of all influenza samples analyzed by the laboratory beginning with the epidemic of 1915–1916 identified *B. influenzae* in “50 to 90 per cent of the cases.”¹ In September and October of 1918, Roos specifically examined 33 specimens from cases of clinical influenza characterized by a sharp onset and isolated *B. influenzae* from 27 (82 percent), although streptococci and pneumococci were also commonly present, being found in 25 (76 percent) and 20 (61 percent) of the specimens, respectively. Although *B. influenzae* could not be reproducibly isolated from all cases of influenza examined, Roos and others placed little significance on the



Demonstration at the Red Cross Emergency Ambulance Station in Washington, D.C., during the influenza pandemic of 1918, c. 1918, Library of Congress, Prints & Photographs Division

negative findings, ascribing them to improper specimen collection or culture technique.² Nevertheless, the inconsistent presence of *B. influenzae* in patient samples, its presence in healthy individuals, and the isolation of other types of bacteria from influenza patients cast doubt on the theory that Pfeiffer's bacillus was the cause of influenza.

William H. Park (AAI 1916, president 1918), laboratory director, New York City Board of Health, Division of Pathology, Bacteriology,

and Disinfection, contended that, to establish etiological significance, it was not sufficient merely to establish the presence of Pfeiffer's bacillus in all (or nearly all) cases of the influenza but that it was also necessary to show that the same strain or type was present in all cases. Under the direction of Park, Eugenia Valentine (AAI 1920) and Georgia M. Cooper (AAI 1920) injected rabbits with cultures of *B. influenzae* and tested each antiserum against the same (homologous) culture and against other cultures of *B. influenzae* isolated from the lung, larynx, or trachea of influenza patients.³ They were surprised to find a multiplicity of strains and could conclude only that “*B. influenzae* is not the primary etiological agent in epidemic influenza.” The lack of a “hypothetical pandemic strain” was later confirmed by similar methods by other investigators, including Arthur F. Coca (AAI 1916, secretary-treasurer 1918–1945, editor-in-chief 1920–1948) and Margaret F. Kelley of New York Hospital and Cornell University.⁴ Other papers, however, presented contradictory findings. In one such paper, F. M. Huntoon (AAI 1918) and S. Hannum demonstrated that antiserum protected mice from heterologous strains of *B. influenzae*.⁵ So it was that, long after the pandemic subsided, uncertainty remained about whether this microorganism was the primary cause of influenza or whether it was a secondary opportunistic invader.

Despite the uncertainty surrounding the cause of influenza, the lethality of the 1918 outbreak lent particular urgency to the question of prevention, and a number of investigators worked to develop a vaccine against the disease. During the height of an influenza epidemic occurring in New Orleans in the fall of 1918, Charles W. Duval and William H. Harris of Tulane University vaccinated approximately five thousand individuals with a chloroform-killed *B. influenzae* preparation.⁶ They reported that only 3.3 percent of those vaccinated developed influenza, compared with 41 percent of the unvaccinated control group. Duval and Harris concluded that, although the number of vaccinated persons was few, the results were “interesting and significant from the standpoint of prophylaxis.” In New York City, Park, in collaboration with other members of an influenza commission and the workers of the New York City Department of Health, undertook a comprehensive study of acute respiratory infections—



Street car conductor in Seattle not allowing passengers aboard without a mask, c. 1918, National Archives at College Park, College Park, MD

work that was funded through a grant from the Metropolitan Life Insurance Company. The first issue of *The Journal of Immunology* from 1921 (vol. 6, no. 1) was dedicated exclusively to this topic and the resulting series of papers.⁷ As part of this series, Park and his colleagues tested combined vaccines made from *B. influenzae* and strains of streptococcus, pneumococcus, and staphylococcus on 1,536 employees of the Metropolitan Life Insurance Company.⁸ Their results were somewhat less striking than the findings of Duval and Harris, as they found no difference in respiratory disease overall (including influenza) between the inoculated and control groups. However, it was noted that the vaccinated group showed the “beneficial influence” of a lower incidence of pneumonia.

The cause of influenza would not be definitively resolved until the 1930s, with the isolation of swine influenza virus by Shope⁹ and the subsequent isolation of human influenza virus by Smith, Andrewes, and Laidlaw.¹⁰ Whereas Pfeiffer’s hypothesis regarding the bacterial cause of influenza was ultimately proven incorrect, it was generally agreed then, as now, that most of the deaths from the 1918–1919 influenza pandemic were due to secondary bacterial infections¹¹—and that some of the early vaccines could have, in fact, prevented the rate of bacterial pneumonia and death from the disease.¹²

Modern influenza research continues to be presented in *The Journal of Immunology* nearly one century after these early papers appeared in the wake of the 1918 pandemic. Topics of research include the role of innate immune defenses in protection, the specificity of the T cell memory response, and mechanisms for improving vaccination, among others. Contemporary papers examine the immune response to recent strains, including swine-origin H1N1 influenza virus, the cause of the 2009 pandemic, and highly pathogenic avian H5N1 influenza viruses, speculated to be the possible source of a new pandemic. Much research remains to be done to fully staunch infection and death from seasonal outbreaks and future pandemics of the disease, but, if recent research is a fair indicator of future initiatives, immunology as a field will yield key findings for understanding influenza and limiting the menace it poses to public health.

¹ C. Roos, “Notes on the Bacteriology, and on the Selective Action of *B. influenzae* Pfeiffer,” *The Journal of Immunology* vol 4 (1919): 189–201.

² For instance, Roos pointed out that *B. influenzae* is “seldom found in the specimens of nasal secretions.” He further noted that he, as a frequent sufferer of common colds, “has been able to demonstrate this fact repeatedly on himself.”

³ Eugenia Valentine and Georgia M. Cooper, “On the Existence of a Multiplicity of Races of *B. influenzae* As Determined by Agglutination and Agglutinin Absorption,” *The Journal of Immunology* vol 4 (1919): 359–379.

⁴ A.F. Coca and M.F. Kelley, “A Serological Study of the Bacillus of Pfeiffer,” *The Journal of Immunology* vol 6 (1921): 87–101.

⁵ F.M. Huntoon and S. Hannum, “The Role of *Bacillus influenzae* in Clinical Influenza,” *The Journal of Immunology* vol 4 (1919): 167–187.

⁶ C.W. Duval and W.H. Harris, “The Antigenic Property of the Pfeiffer Bacillus As Related to Its Value in the Prophylaxis of Epidemic Influenza,” *The Journal of Immunology* vol 4 (1919): 317–330.

⁷ W.H. Park, A.W. Williams, and C. Krumwiede, “Microbial Studies on Acute Respiratory Infection with Especial Consideration of Immunological Types,” *The Journal of Immunology* vol 6 (1921): 1–4. For more on Anna W. Williams, see “Anna Wessels Williams, M.D.: Infectious Disease Pioneer and Public Health Advocate,” *AAI Newsletter*, March/April 2012, pp. 50–51.

⁸ A.I. Von Sholly and W.H. Park, “VII. Report on the Prophylactic Vaccination of 1536 Persons Against Acute Respiratory Diseases, 1919–1920,” *The Journal of Immunology* vol 6 (1921): 103–115.

⁹ R. Shope, “Swine Influenza. III. Filtration Experiments and Etiology,” *The Journal of Experimental Medicine* vol 54 (1931): 373–385.

¹⁰ W. Smith, C. Andrewes, and P. Laidlaw, “A Virus Obtained from Influenza Patients,” *Lancet* vol 2 (1933): 66–68.

¹¹ D.M. Morens, J.K. Taubenberger, and A.S. Fauci, “Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness,” *The Journal of Infectious Diseases* vol 198 (2008): 962–970.

¹² Y. Chien, K.P. Klugman, and D.M. Morens, “Efficacy of Whole-Cell Killed Bacterial Vaccines in Preventing Pneumonia and Death during the 1918 Influenza Pandemic,” *The Journal of Infectious Diseases* vol 202 (2010): 1639–1648.

Anna Wessels Williams, M.D.

Infectious Disease Pioneer and Public Health Advocate

Women have always figured prominently in immunology and in the American Association of Immunologists (AAI). In fact, two of the 54 charter members of AAI were women. During the first 30 years of the association's existence, a total of 55 women were elected to AAI membership.¹ While women remained a minority within AAI, their numbers rose steadily until, by 1940, they comprised 44 of the society's 350 active members. Among these early women members, Anna Wessels Williams, AAI 1918, like Elise L'Esperance profiled in the January-February issue of the *AAI Newsletter*, is one of a number who stand out for their enduring contribution to immunology and to the foundation of AAI. Her legacy in the burgeoning field of immunology includes breakthroughs in the treatment of diphtheria and the diagnosis of rabies. And texts that she co-authored helped to define how generations of researchers and clinicians would conduct research, as well as assist the general public in understanding infectious diseases. We profile her below. Watch for AAI profiles of other pioneering women immunologists to appear in print and online at aai.org/about/history.²

Anna Wessels Williams (1863–1954) was already a highly regarded medical and public health researcher at the laboratory of the New York City Department of Health, when she was elected to AAI membership in 1918. Born in Hackensack, New Jersey, into the family of a private-school teacher, Williams is said to have become fascinated by science when she first peered into a school microscope at age 12. After graduating from a local public high school, she enrolled in the New Jersey State Normal School and seemed destined for a career as a school teacher. For the two years following her graduation in 1883, she did, in fact, teach school.

In 1887, however, Williams's life was to change course. In that year, her sister Millie narrowly escaped death, giving birth to a stillborn child. Struck by the ineffectiveness of the medical treatment received by Millie, Williams became intensely focused on a career in medicine. She resigned from her teaching position to enroll in the Woman's Medical College of the New York Infirmary later that year.

Williams received her M.D. in 1891 from the Woman's Medical College and interned at the New York Infirmary, where she remained as an instructor in pathology and hygiene. Although the exact dates cannot be confirmed, Williams is known to have traveled to Europe



Anna Wessels Williams
(Photo: the Schlesinger Library, Radcliffe Institute, Harvard University)

"Her legacy in the burgeoning field of immunology includes breakthroughs in the treatment of diphtheria and the diagnosis of rabies. And texts that she co-authored helped to define how generations of researchers, clinicians, as well as the general public understood infectious diseases."

to continue her medical training in Vienna, Heidelberg, Leipzig, and Dresden during the years 1892 and 1893.

In 1894, after her return to New York City, she volunteered at the recently opened diagnostic laboratory of the New York City Department of Health, where she would work for the next 39 years.³

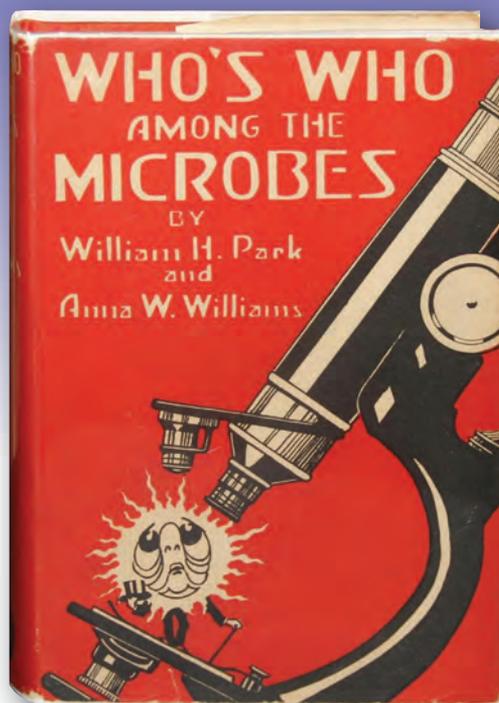
At the time she entered the laboratory, diphtheria had reached near-epidemic levels in the city and was especially high among children from poor families. In her first year at the lab, she began a collaborative research project with the director, William H. Park, AAI 1916 (AAI president, 1918), to eradicate the disease. Their objective was to create a higher-yield antitoxin than was currently available. They would seek to build upon the work of Emil von Behring, who, in 1890, had developed the first successful serum therapy to treat diphtheria.⁴ Though the antitoxins that he created were successful—earning him the first Nobel Prize in Physiology or Medicine in 1901—their low yield meant that many patients were still denied access to the therapy.

While still a volunteer, Williams experienced a breakthrough in the search for a higher-yield antitoxin. Working alone in the lab, with Park away on vacation, she isolated and identified a new strain

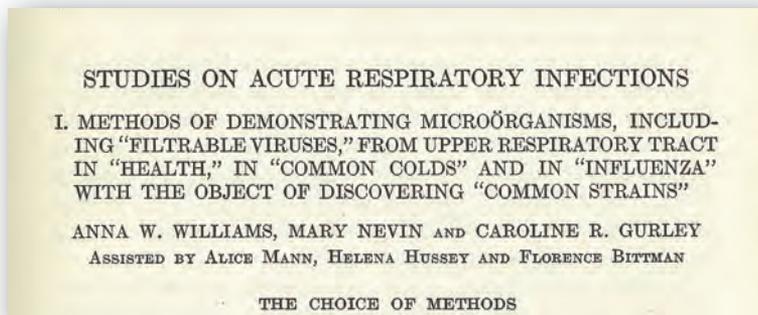
1. AAI memberships comprised just two categories in these early years—Active and Honorary. Both were elected. All members were practicing or retired researchers and clinicians. The majority of the members had either an M.D. or Ph.D. degree. The Trainee membership category was first formally offered in 1983.
2. All membership statistics are taken from election information on AAI Council reports. As no election records exist for 1919, the above statistics are inclusive for 1913–1918 and 1920–1942. AAI Archives.
3. The New York City Department of Health's laboratory was originally opened in 1892 as a temporary emergency laboratory for a cholera outbreak in the city. Laboratory operations were continued and expanded the following year, and it officially became the first municipal laboratory in the United States.
4. In 1884, Friedrich Loeffler discovered the causative organism (*Corynebacterium diphtheriae*).

from a mild case of tonsillar diphtheria. The strain, later to be named Park-Williams No. 8 (commonly called Park 8), proved crucial to the development of effective high-yield antitoxin.⁵ Within just one year, the antitoxin was in mass production and public health departments were distributing it free of charge to physicians in the United States and Great Britain. Although it was Park who was given the recognition for the discovery of the Park-Williams No. 8 strain, Williams stated that she had no regrets about the presumed credit going to her mentor and collaborator, as she was “happy to have the honor of having my name thus associated with Dr. Park.”⁶

In 1895, Williams was hired as a staff member of the laboratory and, in 1896, was able to take a sabbatical to carry out research on an antitoxin for scarlet fever at the Pasteur Institute. In Paris, her work on scarlet fever yielded no dramatic results, but the trip was fruitful in another area of research. Having spent some of her time at the Pasteur involved in its rabies research, she returned to New York intent upon improving rabies prevention and diagnostics. By 1898, she was able to create an effective vaccine that could be mass produced in the United States. This was a major step in the prevention of rabies, but many patients were still succumbing to the disease because of the lengthy, 10-day-or-longer diagnostic period.



Cover for the 1937 edition of *Who's Who among the Microbes* (Photo: The Reluctant Bookseller)



Anna Wessels Williams's first published scientific article in The JI (J. Immunol. 1921. 6(1): pages 5–24); one of a series of papers from the laboratory of the New York City Department of Health concerning the etiology and prevention of the pandemic influenza

Williams turned her attention to a search for some means of detecting the disease much earlier in its occurrence and began studying the brains of infected animals. Her work led to a rabies diagnostic breakthrough within the decade resulting from her discovery of abnormal brain cells in rabid animals. She was not, however, to be generally recognized for this important stride forward, as she was not the first to publish a journal article about the brain cell abnormalities. At the same time that she was performing her research in New York, Adelchi Negri, an Italian pathologist, was studying the same phenomenon in his lab at the University of Pavia. Although it is held that Williams was the first to recognize this distinct brain-cell structure in rabid animals, she is

said to have “cautiously waited” to publish her results.⁷ Meanwhile, Negri published his seminal paper in 1904 and became widely recognized for the breakthrough.⁸ The abnormal cells, known as Negri bodies, bear his name.

Williams continued her rabies research, focusing on the use of brain tissue stains in diagnostics. In 1905, she developed a diagnostic test that yielded results in minutes rather than days.⁹ Williams’s test quickly became the standard rabies test and remained so for the next 30 years. It was not to be improved upon until the late 1930s.

In 1905, Williams was promoted to the position of first assistant director of the diagnostic laboratory. In her position, she directed research on a range of urgent public health issues, including influenza, venereal diseases, polio, and trachoma. During the First World War, with the laboratories of top American researchers focused intensely on influenza, Williams was one of a very few female scientists working to identify the pathogen

- For a modern study of Park-Williams 8 strain see Lesley M. Russell and Randall K. Holmes, “Highly toxigenic but avirulent Park-Williams 8 strain of *Corynebacterium diphtheriae* does not produce siderophore,” *Infection and Immunity* 47, no. 2 (1985): 575–578.
- National Institutes of Health, “Dr. Anna Wessels Williams,” *Changing the Face of Medicine*, National Library of Medicine, www.nlm.nih.gov/changingthefaceofmedicine/physicians/biography_331.html (accessed 7 February 2011).
- Elizabeth D. Schafer, “Anna Wessels Williams,” *American National Biography Online*, www.anb.org (accessed 7 February 2011).
- Adelchi Negri, “Contributo allo studio dell’eziologia della rabbia,” *Bollettino della Società medico-chirurgica di Pavia* 2 (1904): 88–115.
- Anna Wessels Williams and May Murray Lowden, “The Etiology and Diagnosis of Hydrophobia,” *Journal of Infectious Diseases* 3, no. 3 (1906): 452–448.

responsible for the pandemic. The women researchers were largely limited to lab work, analyzing specimens forwarded by male scientists from military bases. Williams, however, was the exception. With Park, she was summoned to Camp Upton on Long Island in September 1918 to investigate the disease on the front lines of a new outbreak.¹⁰

On another front, her research on trachoma resulted in a more accurate diagnostic test and opportunity to spare the eyesight of many schoolchildren infected by the disease. As with diphtheria, her work on trachoma proved greatly beneficial for the urban poor.¹¹

Outside of the laboratory, Williams lived a life far removed from the cautious calibrations and sometimes mundane routine of the laboratory. She seems to have invited risks, as she was known to love being a passenger in pre-First World War airplanes, especially with stunt fliers. And she appeared determined to replicate the excitement felt for a scientific discovery in the thrill of speeding in her car through the streets of New York City—or so the many documented speeding tickets would suggest.¹²

“Outside the laboratory, Williams lived a life far removed from the cautious calibrations and sometimes mundane routine of the laboratory. She seems to have invited risks, as she was known to love being a passenger in pre-First World War airplanes, especially with stunt fliers. . . .”

In 1934, despite an outpouring of support and a petition campaign by scientists, clinicians, and other public health professionals, Williams was forced to step down from her position at the bench and enter retirement. At 71, she had exceeded the established mandatory retirement age of 70 for city employees.¹³

Beyond her achievements in the laboratory, Williams co-authored two books with Park that helped define the way contagious diseases were to be understood: *Pathogenic Micro-organisms Including Bacteria and Protozoa: A Practical Manual for Students, Physicians and Health Officers* (1905) and *Who's Who among the Microbes* (1929). The former was so widely referenced that it was known among researchers and clinicians alike simply as “Park and Williams.”



Anna Wessels Williams
(Photo: the Library of Congress)

“Although she may have never received the renown granted a male researcher for the same discoveries, Williams’s research and publications informed the work of generations of scientists, male and female.”

By 1939, 11 editions of the text had been published. (At last, one of her contributions to science would bear her own name.) Their second text, *Who's Who among the Microbes*, was one of the first biomedical reference books written for the general public.

Throughout her long career, Williams served in leadership roles and received numerous honors and awards. Among them were her posts as president of the Woman’s Medical Association (1915) and as the first female chair of the American Public Health Association’s Laboratory Section (1932). Through her position at the diagnostic laboratory, Williams made seminal discoveries that advanced the medical understanding of diphtheria and rabies and, in doing so, saved countless lives. With her election to AAI in 1918, she not only was accorded recognition by her peers, but she also lent honor to the young organization.

Although she may have never received the renown granted a male researcher for the same discoveries, Williams’s research and publications informed the work of generations of scientists, male and female. And her distinction in her career inspired confidence for the growing number of female researchers and clinicians entering the field. Upon her retirement, New York City Mayor Fiorello LaGuardia accurately summed up Anna Wessels Williams’s career: She was “a scientist of international repute.”¹⁴

10. For more detail on Williams’s influenza research during the First World War, see John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (Penguin Books: New York, 2005).

11. Trachoma is an eye infection characterized by a telltale roughening of the inner surface of the eyelid, and, if left untreated, causes blindness. In turn of the century America, trachoma was designated a “dangerous and contagious disease” by the surgeon general. As such, beginning in 1905, all immigrants were screened for it upon entering the country, and those who had it were sent back to their country of origin. As it was highly communicable, trachoma was also a growing problem in the poor and immigrant communities, especially among children. Quote from Howard Markel, *When Germs Travel: Six Major Epidemics That Have Invaded America and the Fears They Have Unleashed* (Vintage: New York, 2004), 88. See also Alan M. Kraut, *Silent Travelers: Germs, Genes, and the “Immigrant Menace”* (Johns Hopkins University Press: Baltimore, 1994); Anna Wessels Williams, “A Study of Trachoma and Allied Conditions in the Public School Children of New York City,” *The Journal of Infectious Diseases* 14, no. 2 (1914): 261–337.

12. Barry, 272–273.

13. *The New York Times*, “Physicians Plead for Dr. Williams,” 28 March 1934; *The New York Times*, “City Acts to Oust Woman Scientist,” 14 March 1934.

14. *The New York Times*, “94 Retired by City; 208 More Will Go,” 24 March 1934. For additional resources see: Schafer, “Anna Wessels Williams”; National Institutes of Health, “Dr. Anna Wessels Williams”; Marilyn Bailey Ogilvie, Joy Dorothy Harvey, eds., “Anna Wessels Williams (1863–1954),” *The Biographical Dictionary of Women in Science: L-Z* (Routledge: New York, 2000), 1380–1381; *The New York Times*, “Anna W. Williams, Scientist, Is Dead,” 21 November 1954; King-Thom Chung, *Women Pioneers of Medical Research: Biographies of 25 Outstanding Scientists* (McFarland & Company, Inc: Jefferson, NC, 2010), 48–51.

100 Years of AAI: A Look Back at Two Early Immunologists in Hawaii

On the occasion of its centennial meeting in Honolulu, AAI reflects on the association's long ties to Hawaii.

“Hawaii,” for most AAI members, including those who attended IMMUNOLOGY 2013™, conjures up images of vast white sand beaches and palm trees swaying in gentle sea breezes. These Edenic images, however, belie the islands’ history as a setting for pioneering immunological research and their longstanding connection to AAI.

In fact, one Hawaiian physician, Archibald N. Sinclair, was among the 52 charter members of AAI in 1913. Sinclair, an established authority on tuberculosis, pioneered an immunological-based method for its treatment.

Another early AAI member in Hawaii, Nils P. Larsen, spearheaded massive reforms to improve public health on the islands as early as the 1920s.

We profile below the lives and careers of these two distinguished early AAI members.

Archibald Neil Sinclair, M.B.C.M., AAI '13 Career Overview

Archibald N. Sinclair was born in New York City on January 20, 1871, just two years after his parents emigrated from Scotland to the United States. Before he was 10 years old, the family moved to Hawaii, when his father, a building contractor, was hired to help build ‘Iolani Palace, the residence commissioned by King Kalākaua, the last Hawaiian king. The family remained in Honolulu after construction of the palace was completed in 1882, and Sinclair attended Oahu College (now known as the Punahou School), a college preparatory school that includes President Barack Obama among its alumni.

After graduating from high school in 1889, Sinclair moved to his parents’ homeland and studied medicine at the University of Glasgow. Upon earning his M.B.C.M.



‘Iolani Palace, 1898

Hawaii State Archives, Digital Collections, Photograph Collection

(Bachelor of Medicine, Master of Surgery) in 1894, he practiced medicine in Yaxley, England, for three years before returning to Hawaii. He began a private practice in Waianae, Oahu, in 1897, but by 1901, he had fully dedicated himself to public health. That year, he was named city physician of Honolulu, a position he held until 1908, and was appointed the first medical superintendent of the Leahi Home, the recently opened tuberculosis sanitarium in Honolulu, where he was to spend the rest of his career. He served

concurrently as acting assistant surgeon for the U.S. Public Health Service from 1900 to 1919 and as physician in charge of the tuberculosis bureau and the bacteriological department of the Territorial Board of Health from 1911 to 1916. Resuming his private practice in 1916 while retaining his position at the Leahi Home, Sinclair continued to specialize in the treatment of tuberculosis and other pulmonary ailments until his death on October 21, 1930.¹

Well-respected among Hawaiian physicians, Sinclair was twice elected president of the Hawaiian Territorial Medical Society, first from 1907 to 1908 and again from 1926 to 1927.

Making the Case for Tuberculin

A remarkable clinician whose case studies were reported in the *Journal of the American Medical Association*,² Sinclair garnered a national reputation for his success in treating tuberculosis with tuberculin. He first presented his “Case for Tuberculin” before the Hawaiian Territorial Medical Society in 1914.³ The use of tuberculin to treat pulmonary tuberculosis was one of the most controversial immunological issues of the day and had been among the topics debated at the first AAI annual meeting held

1. “Sinclair, Archibald N.,” *Men of Hawaii: A Biographical Reference Library, Complete and Authentic, of the Men of Note and Substantial Achievement in the Hawaiian Islands*, vol. 2, ed. by John William Siddall (Honolulu: Honolulu Star-Bulletin, 1921), 363; “Archibald Neil Sinclair,” In Memoriam—Doctors of Hawaii—XI, *Hawaii Medical Journal and Inter-Island Nurses’ Bulletin* 17, no. 2 (1957): 152; Gwenfread Allen, *The Story of Leahi: Fifty Years of Service, 1901–1951* (Honolulu: Trustees of Leahi Hospital, 1951), 10; “Dr. Archibald Neil Sinclair House,” Nomination Form, National Register of Historic Places, U.S. National Park Service, <http://pdfhost.focus.nps.gov/docs/NRHP/Text/83003557.pdf>.

2. A. N. Sinclair, “Yersin-Roux Serum in the Treatment of Plague,” *Journal of the American Medical Association* 56, no. 5 (1911): 332–35; A. N. Sinclair, “The Diazo and Urochromogen Reactions in Pulmonary Tuberculosis,” *Journal of the American Medical Association* 66, no. 4 (1916): 247–48.

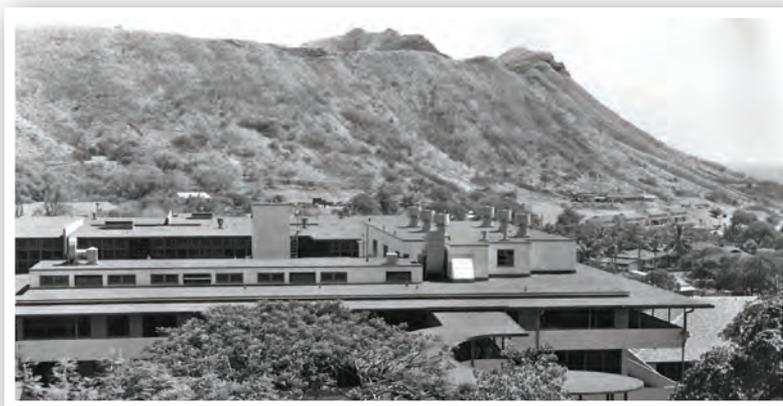
3. A. N. Sinclair, “The Case for Tuberculin,” *Transactions of the Medical Society of Hawaii* 23 (1914): 79–97.

in Atlantic City, New Jersey, the same year that Sinclair reported his positive findings.⁴ The reason for the controversy was that prior attempts to use tuberculin as a treatment, notably those by Robert Koch in the 1890s, had low success rates and often produced unexpected, negative outcomes, even death. Sinclair conceded that tuberculin treatment was a very complicated, precise process that was ineffective if not administered properly and “in inexperienced hands, even dangerous.”⁵

He cited two schools of thought on administering tuberculin. He dubbed one method the “rules on the bottle method” for treating each patient with a fixed, and often too intense, recommended dosage. He referred to the other method as the “immunizing” method, which he attributed to Sir Almroth Wright (AAI ’14).⁶ Sinclair, having spent four months at St. Mary’s Hospital in London observing Wright prepare and administer tuberculin in 1911, had further refined the process at Leahi Home.⁷ Sinclair’s therapeutic immunizing method involved administering small, regulated tuberculin doses over a long interval and varying those doses based on Wright’s “opsonic index,” which measured the opsonin content in patients’ blood. There was no single dosage that was suitable for all patients nor could tuberculin be expected to cure all patients. Such promises, Sinclair asserted, were “what makes the patent medicine man his living” and were not made by responsible medical practitioners.⁸

Nevertheless, he was convinced that when meticulously administered, tuberculin produced incomparable results. He reported that 67.6 percent of patients who had received tuberculin treatments were able to leave Leahi and return to work, a dramatic increase from the 27.2 percent able to do so before he began administering tuberculin.⁹ Sinclair encountered harsh opposition from a Hawaiian colleague who declared that Wright’s opsonic index was “not accepted in this country,”¹⁰ but he remained sanguine about the prospects for tuberculin treatment and, in May 1916, traveled to Washington, D.C., to report his findings at the third AAI annual meeting.¹¹

Despite Sinclair’s efforts and optimism, his method of treating tuberculosis was never widely adopted. Most clinicians were concerned that the potential was too great for negative side effects from improper administration.¹² According to Arthur Silverstein (AAI ’63), although



Sinclair Building on the Leahi Hospital campus, built in 1949 and named for Archibald N. Sinclair

Courtesy of Leahi Hospital

Wright’s opsonic index was initially met with a great deal of enthusiasm among some immunologists, particularly those in his native England, “the techniques proved so difficult and unreproducible in practice as to become unfashionable within a decade.”¹³

Nevertheless, Sinclair could take pride in the success he had encountered while treating tuberculosis patients at the Leahi Home. Reflecting on the progress that had been made in the treatment of tuberculosis in the first decade of the twentieth century alone, he noted, “One familiar with the [Leahi] Home and its conditions during the past few years cannot but be struck by the change—a few years ago people looked upon it as the last resort of the hopeless—a walk through its wards encountered almost bed-ridden patients entirely; now it is coming to be looked upon as the hope and salvation of the afflicted, and a walk through its wards will frequently show not a single patient in bed—or at the worst of times but an extremely small percentage of bedridden patients.”¹⁴



Archibald N. Sinclair, ca. 1927

Courtesy of Queen’s Heritage Collection, Queen’s Medical Center

4. “Science at the First AAI Annual Meeting,” *AAI Newsletter*, May/June 2012, 30.

5. Sinclair, “The Case for Tuberculin,” 79.

6. *Ibid.*, 86.

7. *Ibid.*, 85; Allen, *The Story of Leahi*, 12–13, 15.

8. Sinclair, “The Case for Tuberculin,” 97.

9. *Ibid.*, 80.

10. J. T. McDonald, “Discussion,” in *ibid.*, 94.

11. Evidently, tuberculin treatment proved slightly less successful in the two-year interim between presenting his findings at the Medical Society of Hawaii meeting and the AAI meeting. He now reported a success rate of 50.1 percent compared with his earlier rate of 67.6 percent. Abstract of A. N. Sinclair, “Treatment of Tuberculosis Pulmonalis by Tuberculin,” in “Proceedings of the American Association of Immunologists: Third Annual Meeting, Held in Washington, D. C. May 11, 1916,” *The Journal of Immunology* 1, no. 4 (1916): 489–90.

12. “Science at the First AAI Annual Meeting,” 30.

13. Arthur M. Silverstein, *A History of Immunology*, 2nd ed. (New York: Elsevier, 2009), 38.

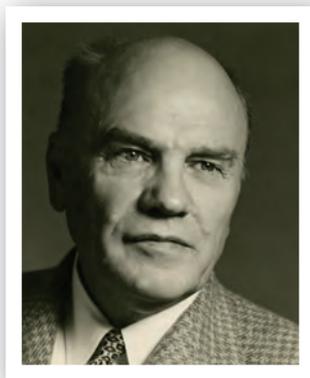
14. A. N. Sinclair, *Fighting the Great White Plague* (Honolulu: Hawaiian Gazette Co., 1914), 11.

Nils Paul Larsen, M.D., AAI '23

A Religious Upbringing

Although Nils P. Larsen did not call Hawaii home until well into adulthood, his impact on Hawaiian medicine and public health was no less significant than Sinclair's. Born in Stockholm, Sweden, on June 15, 1890, Larsen was the sixth of seven children born to a tailor struggling to support his growing family. Overpopulation and successive crop failures were impoverishing life in Sweden, impelling approximately 330,000 Swedes to immigrate to the United States during the 1880s. When Nils was only three years old, the Larsen family joined the ranks of those who hoped to find a better life in the New World. After settling briefly in Peeksville, New York, Nils's father, a devout man, relocated the family to Bridgeport, Connecticut, where he helped start a church for the Swedish Evangelical Mission Covenant, a Lutheran denomination founded in Chicago in 1885. While attending public school in Bridgeport, Larsen held part-time jobs to help support his family, including work in a steel mill during the summers of his high school years.¹⁵

Larsen attended the Massachusetts Agricultural College (now the University of Massachusetts, Amherst), where he intended to study forestry. Although he began to abandon the formal religious dogmas embraced by his pious father, Larsen remained committed to the Christian ideal of helping others that lay at the heart of the Social Gospel movement of the era. He became actively involved in student religious groups on campus, including the YMCA and the College Christian Association. While attending one religious conference, at which missionaries relayed accounts of their travels, Larsen learned that there was only one doctor for every one million people in China. He decided then that he wanted to become a physician, not out of any special yearning to solve scientific problems but out of his deep-seated commitment to social justice and community service.¹⁶



Nils P. Larsen, ca. 1955
Courtesy of Queen's Heritage
Collection, Queen's Medical Center

Early Career, War, and Marriage

After graduating from Massachusetts Agricultural College in 1913, Larsen attended Cornell Medical School in New York City, earning his M.D. in 1916. He then interned in the pathology department at New York Hospital and took additional courses in biological chemistry at Columbia University. When the United States entered the First World War in April 1917, Larsen was commissioned as a first lieutenant in the Medical Corps of the U.S. Army and was deployed to Belgium the following May. While in Belgium, he received news that his younger sister had died of tuberculosis. Absorbing this loss during the influenza pandemic that ravaged families across the globe likely motivated his later work to combat tuberculosis.

In the spring of 1919, Larsen was promoted to major, awarded the Silver Star for his valor during combat, and released from active duty. That summer, he made his first trip to Hawaii, where he visited his older brother David, a plant pathologist, who was now a manager of a sugar plantation. Following his vacation, he returned to New York to teach at Cornell Medical School and serve as assistant visiting physician in pediatrics at Bellevue Hospital. These years in New York, from 1919 to 1922, proved to be some of Larsen's most productive for clinical research and writing. He published case studies on allergic reactions, asthma, and pneumonia in the *Journal of the American Medical Association* and *The Journal of Immunology*.¹⁷

In September 1921, Larsen married Sara "Sally" Lucas, whom he had met two years earlier during his Hawaiian vacation. Although the two had not kept in touch following Larsen's return to New York, Sally was apparently impressed by Larsen during his visit to Hawaii and contacted him upon her arrival in New York from Honolulu to start a confectionary. The extent to which the confectionary materialized is unclear, but, within months, the couple wed.

Sally's mother appears to have been equally decisive and proactive as her daughter. Upon learning of an opening for a pathologist at Queen's Hospital in Honolulu, she mentioned Larsen to the administrators. If she was seizing upon a possible means of bringing her daughter back to Hawaii, she succeeded. Larsen was offered the position in July of 1922 and promptly accepted it.¹⁸

15. Janine A. Powers, "Worlds Beyond Medicine: Nils P. Larsen's Impact on Hawai'i," *Hawaiian Journal of History* 39 (2005): 92–93.

16. *Ibid.*, 93–94.

17. Russell L. Cecil and Nils P. Larsen, "Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia," *Journal of the American Medical Association* 79, no. 5 (1922): 343–49; Nils P. Larsen, Royce Paddock, and H. L. Alexander, "Bronchial Asthma and Allied Conditions: Clinical and Immunological Observations," *The Journal of Immunology* 7, no. 2 (1922): 81–95; Nils P. Larsen, A. V. R. Haigh, Harry L. Alexander, and Royce Paddock, "The Failure of Peptone to Protect against Anaphylactic Shock and Allergic Conditions," *The Journal of Immunology* 8, no. 5 (1923): 409–24.

18. Powers, "Worlds Beyond Medicine," 96; Janine A. Powers, "From Medicine to Art: Nils Paul Larsen (1890–1964)" (Ph.D. diss., University of Hawaii, 2003), 22.

At Queen's Hospital

Larsen immediately impressed the administrators of Queen's Hospital. In 1924, he was appointed the hospital's medical director, a position he held until 1942. Named for Queen Emma, its most enthusiastic champion, Queen's Hospital was founded in 1859 to provide medical care to a rapidly dwindling Hawaiian population.

Occupying a major port of call on trade routes across the Pacific, the Hawaiian population was, at that time, besieged by diseases borne by foreigners, most recently a smallpox epidemic that swept across the islands in 1853.¹⁹ At the time of Larsen's appointment more than 60 years later, the hospital had failed to keep pace with the medical advances on the mainland.

Larsen immediately set out to modernize Queen's Hospital. His first reform was to arrange weekly clinics in which medical practitioners from all over the island came together to share and discuss their cases, including the week's deaths. Often, Larsen recruited notable visiting physicians to lecture and consult with the local doctors, and word of the effectiveness of his clinics began to spread nationally, earning Larsen praise in the pages of the *New York Times*.²⁰ He also significantly improved living conditions for the nurses—usually women who were recruited from plantations—raising \$125,000 for the construction of new nurses' quarters in 1931.²¹

Reforming Hawaiian Public Health

Larsen's reforms extended well beyond the walls of Queen's Hospital. He made several significant contributions to improving public health in Hawaii. Shocked by the high infant-mortality rate on the islands, Larsen spearheaded a clean-milk campaign in November 1922. His investigations into the Hawaiian milk industry uncovered widespread unsanitary conditions and resulted in new laws regulating milk production. The successful campaign became a national story when it was reported years later in *Reader's Digest*.²² In the late 1920s, he also called for "preventorium," camps where pre-tubercular children would receive medical care and be provided with a proper diet. With the support of Archibald Sinclair and others at Leahi Home, the first preventorium in Hawaii opened its doors in 1930.²³



Queen Emma, ca. 1880

Photo by A. A. Montano; Hawaii State Archives, Digital Collections, Photograph Collection

Perhaps Larsen's greatest reforms came in his work with the Hawaiian Sugar Planters' Association. In 1928, he criticized the planters for allowing their workers to live in substandard conditions. Improvements in living conditions and diets could prevent the suffering and even death caused by diseases such as beriberi and gastroenteritis, argued Larsen. He soon convinced planters that these reforms were not only a moral obligation but also a sound economic investment. New meal plans were implemented, and health centers were established on plantations where workers could receive treatment and consultation on nutrition, hygiene, and even birth control.²⁴

A Change of Direction

In 1939, Larsen contracted typhus and was hospitalized for 20 days. Shortly after his recovery, he wrote to Hans Zinsser (AAI '17, president 1919–1920) at Columbia University, an authority on typhus and author of *Rats, Lice and History*. The playfully familiar tone of his letter suggests that Larsen knew Zinsser from his time in New York: "I had occasion recently to meet your good friend with whom you have been so intimately associated . . . throughout your professional life—namely typhus fever."²⁵

The typhus left Larsen with angina, for which he decided to seek treatment in Boston. The decision was a fortunate one, for he and his wife departed Hawaii on December 5, 1941, just two days before Pearl Harbor was attacked. When he returned in 1942, he stepped down from his position as medical director of Queen's Hospital and began a private practice.

Larsen continued his research and began pursuing new topics, including the effects of diet on aging.²⁶ He also became interested in native Hawaiian medicine, pointing out that the traditional remedies of the *kahuna lapa'au*, Hawaiian medicine men, were often more scientific than those of the nineteenth-century Western doctors who so easily dismissed them as primitive. Larsen even developed a supplement made of taro, a plant

19. Richard A. Greer, "The Founding of the Queen's Hospital," *Hawaiian Journal of History* 3 (1969): 110–45.

20. Russell Owen, "Massie Will Take Stand Again Today," *New York Times*, 18 April 1932, 5; "Cited for Hawaiian Work: Dr. Nils Paul Larsen to Receive Cornell Alumni Award," *New York Times*, 14 April 1952, 21.

21. Powers, "Worlds Beyond Medicine," 100–101.

22. *Ibid.*, 99; Blake Clark, "Plantation Babies Okay Now," *Reader's Digest*, January 1947, 127–30.

23. Powers, "Worlds Beyond Medicine," 99–100.

24. *Ibid.*, 101–104.

25. *Ibid.*, 106.

26. *Ibid.*, 110–11; Nils P. Larsen, "Animal Fat Diet and Atherosclerosis," *Hawaii Medical Journal and Inter-Island Nurses' Bulletin* 14, no. 6 (1955): 485–90; Walter Sullivan, "Survey of 500,000 Will Study Role of Diet in Heart Disease," *New York Times*, 31 August 1961, 1.

common in the traditional Hawaiian diet that he believed promoted dental health.²⁷ Perhaps it was his eagerness to synthesize Eastern and Western traditions that made him popular with Hawaiians and won him election to the 1950 Constitutional Convention charged with preparing for Hawaiian statehood.²⁸

Although he officially retired in 1955, Larsen continued to treat patients until his death of a heart attack, at the age of 73, on March 19, 1964.²⁹



Queen's Hospital, ca. 1925

Courtesy of Queen's Heritage Collection, Queen's Medical Center

Hawaii—A Researcher's Paradise

Speaking before the Hawaii Medical Association at Queen's Hospital in April 1935, Nils Larsen noted, "The type of observations possible here are endless and many of them cannot be made anywhere else in the world."³⁰ Not only Larsen but also Archibald Sinclair before him and dozens of AAI members since have taken advantage of the unique setting Hawaii offers for immunological research. Even immunologists who were far removed from the islands geographically have long benefited from the presence of AAI members there, as when Arthur F. Coca (AAI '16) and Ella F. Grove (AAI '24) obtained tropical pollen samples from Larsen for their "Studies in Hypersensitiveness" in 1924.³¹

Hawaii may be at once an island paradise and, in the words of Larsen, "the best biological test tube in the world."³²

27. Powers, "Worlds Beyond Medicine," 107–10.

28. Arthur V. Molyneux, "Nils Paul Larsen, M.D.," *Hawaiian Medical Journal* 23, no. 5 (1964): 388.

29. Ibid.; Powers, "Worlds Beyond Medicine," 111.

30. Nils P. Larsen, "Cancer," *Transactions of the Hawaiian Territorial Medical Association* 45 (1935): 48–52, quote from 48.

31. Arthur F. Coca and Ella F. Grove, "Studies in Hypersensitiveness. XIII. A Study of the Atopic Reagents," *The Journal of Immunology* 10, no. 2 (1925): 445–64.

32. Larsen, "Cancer," 48.

A Chronological Overview:

300–500 AD—Polynesians first inhabit Hawaiian Islands

1778—British explorer Captain James Cook lands in Hawaii; his published account provides the earliest documentation of European contact with islands

1785—First trading ship lands in Hawaii on way to China; sandalwood trade and whaling soon become major industries

1810—Kamehameha formally establishes Kingdom of Hawaii and proclaims himself king after 15-year struggle with *ali'i* (chiefs)

1819—King Kamehameha II abolishes the *kapu*—the traditional religious and legal system that governed all aspects of Hawaiian life

1820—First Protestant missionaries arrive from the United States

1835—First commercially successful sugar plantation is opened by Ladd and Company

1848—King Kamehameha III enacts the *Mahele*, a land division act that introduces legal provisions for private ownership of land; opens way for rapid growth of sugar plantations

1859—Queen's Hospital, named for Queen Emma, is founded to provide medical care to Hawaiian people

1872—King Kamehameha V dies without heir, ending the House of Kamehameha

1874—Riots during the subsequent succession crisis are suppressed by U.S. and British troops; Kalākaua becomes King of Hawaii

1875—Reciprocity Treaty signed between the United States and Kingdom of Hawaii cedes Pearl Harbor to the United States in return for duty-free importation of Hawaiian sugar into the United States

ca. 1880—Archibald N. Sinclair moves to Hawaii with his family as a young boy

1887—King Kalākaua is forced to sign new constitution that strips monarchy of power by the Hawaiian League, a group of American and British businessmen who favor annexation by the United States

1891—King Kalākaua dies and is succeeded by his sister, Queen Lili'uokalani who calls for new constitution

1893—U.S. Marines arrive in Hawaii at request of the Hawaiian League, making it impossible for Queen Lili'uokalani to continue her rule; although U.S. Congress found no party guilty of overthrow in 1894, Congress issued a joint Apology Resolution in 1993 accepting U.S. responsibility for overthrowing the sovereign kingdom

1894—Republic of Hawaii is established

1897—Sinclair returns to Oahu and opens private practice after spending eight years in the United Kingdom, where he received his medical training

1898—Hawaii is annexed by the United States and becomes the Territory of Hawaii

1901—Sinclair is appointed city physician of Honolulu and the first medical superintendent of the Leahi Home

1919—Nils P. Larsen visits his brother in Hawaii after returning from the First World War

1922—Larsen accepts position as a pathologist at Queen's Hospital and moves to Honolulu from New York; he is soon appointed medical director of the hospital

1930—Sinclair dies in Honolulu at the age of 59

1941—The United States enters the Second World War after the attack on Pearl Harbor

1942—Larsen steps down as medical director of Queen's Hospital and begins private practice

1950—Larsen serves as member of the convention that drafts the Hawaiian constitution in preparation for statehood

1954—Democratic Party takes control of Territorial Legislature and pushes for statehood

1959—Hawaii becomes the 50th state of the United States

1964—Larsen dies of a heart attack in Honolulu at the age of 73

PI in the Scotland Yard of Streptococcal Mysteries

Rebecca Lancefield, Ph.D. (AAI 1933, President 1961–62)

Among early members of the American Association of Immunologists (AAI), few left a more enduring legacy than that of Rebecca Craighill Lancefield. A world-renowned authority on streptococcal bacteria, Lancefield developed the classification system of streptococcus bearing her name and still in use today. Her identification of streptococcal types proved essential to revealing the complexities of the immune response to the bacteria and elucidating streptococci as the primary infectious agent for many diseases—understandings that enabled improved methods for identifying and controlling streptococcal infections. Recognized broadly for her outstanding scientific achievements, Lancefield, in 1961, was elected by her peers to serve as president of AAI, becoming the first woman elected to this office.

Lancefield's distinguished career path was all the more remarkable for having been an indirect one. A number of changes in her life could have diverted her progress, but, at each juncture, she turned perceived interruptions into opportunities.

Early education

Rebecca Craighill was born in Fort Wadsworth, Staten Island, New York, on January 5, 1895, one of six daughters of Colonel William Craighill, U.S. Army Corps of Engineers. A West Point graduate, William married the sister of one of his classmates, Mary Byram Craighill. Mary, an early proponent of female education, encouraged her daughters to devote themselves to their schooling—and with good results.¹ In addition to Rebecca's successful research career, one of Rebecca's sisters became an accomplished physician.



Rebecca Craighill, ca. 1914

Image courtesy of Rockefeller Archive Center

In the fall of 1912, Rebecca entered Wellesley College with the intention of studying French and English literature. She soon became fascinated by her roommate's freshman zoology course, however, and changed her major to zoology. She attacked the subject zealously, taking as many additional courses in biology, including bacteriology, and chemistry as she could while meeting the requirements for graduation.²



Rebecca C. Lancefield, AAI president 1961–62, ca. 1961

Image courtesy of the Center for Biological Sciences Archives, UMBC

By the time of her college graduation in 1916, her father had died, and the family was in financial straits. To help support her mother and younger sisters, she spent her first year out of college teaching mathematics and basic science at a girls' boarding school in Burlington, Vermont. Even as she sent money home, Rebecca managed to put aside a bit toward tuition for further studies.³



Wellesley College, c. 1908—It was here that Lancefield found her passion for science.

Library of Congress, Prints & Photographs Division, Detroit Publishing Company Collection

¹ Judith N. Schwartz, "Mrs. L.," *Research Profiles*, Rockefeller University, Summer 1990, <http://hdl.handle.net/10209/347>.

² Elizabeth M. O'Hern, "Rebecca Craighill Lancefield, Pioneer Microbiologist," *ASM News* 41, no. 12 (1975): 805.

³ *Ibid.*



Oswald Avery, ca. 1929

Image courtesy of the Center for Biological Sciences Archives, UMBC



Alphonse R. Dochez, ca. 1931

Image courtesy of the Center for Biological Sciences Archives, UMBC

In the fall of 1917, she was able to combine her meager savings with a scholarship from the Daughters of Cincinnati for daughters of Army and Navy officers. The scholarship was to help her attend Teachers College, Columbia University, preparing for the conventional occupation of the time for educated, unmarried women. The scholarship, however, did not specify that Rebecca must take her classes at Teachers College, only that she should matriculate there, and so, she took the liberty of enrolling in courses in the Department of Bacteriology at Columbia's College of Physicians and Surgeons (P&S).⁴

Although she was entering the field obliquely, she was beginning her graduate studies in a rarified environment. At the P&S, she entered the department of prominent immunologist and bacteriologist Hans Zinsser (AAI '17, president 1919–20), although, at the time of her arrival, he was stationed in France as part of the U.S. Army Medical Corps. Aware that students in Zinsser's lab were expected "to spend all of their waking hours in class or in the

laboratory,"⁵ Rebecca spent much time in the laboratory at Presbyterian Hospital, typing strains of pneumococci from patients. In addition to her classes, she was encouraged to attend other lectures by distinguished New York scientists. Rebecca was particularly impressed by a lecture given by Oswald Avery (AAI '20, president 1929–30) on the lag phase of pneumococcal cultures.⁶ Upon reading Avery's 1917 articles on the specific soluble substance of pneumococcus,⁷ she decided to look for an analogue in staphylococcus. She now had the topic for her thesis, which she succeeded in completing that same year.⁸

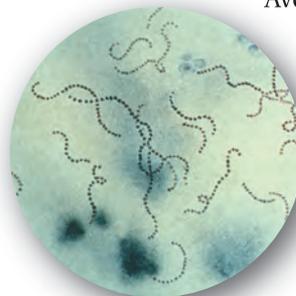
In the spring of 1918, she graduated from Columbia with an M.A., married Donald Lancefield, a zoology graduate student in the laboratory of eminent geneticist Thomas Hunt Morgan at Columbia, and applied for a position at the Rockefeller Institute for Medical Research (RIMR). With her degree in hand, she interviewed with the director, Simon Flexner (AAI '20), who hired her as a technician for Martha Wollstein (AAI '18), who had previously worked closely with Flexner on early experimental polio research and Pfeiffer's bacillus. But Wollstein soon left RIMR to carry out research on the influenza pandemic,⁹ and Flexner suggested that Alphonse R. Dochez (AAI '20, president 1931–32) may have use for Lancefield in his ongoing research under a U.S. Army grant to study streptococcal infections at military bases. She interviewed with Dochez and with Avery, a collaborator on the project, and was quickly taken on as their laboratory technician.¹⁰

Oswald Avery and the techniques of classification

Lancefield's arrival at RIMR in the summer of 1918 occurred just as two transformative events began to change the direction of research for many scientists, including Avery and Dochez. The United States had begun sending troops to the European front for the First World War, and the 1918 influenza pandemic was sweeping the nation. The previous winter, Avery and Dochez had been asked by U.S. Surgeon General William C. Gorgas to put their studies of pneumococcus on hold to consult on a serious outbreak of measles and streptococcal infections at military camps in Texas. It was this shift in focus for

Avery and Dochez that led Lancefield to the study of streptococcus, the organism that would command her attention throughout her career.

Avery and Dochez collected samples of streptococci from the camps in Texas for further study in their New York laboratory. At that time, streptococci had not been classified and were widely



Streptococcus

Image courtesy of the Centers for Disease Control and Prevention

⁴ Maclyn McCarty, "Rebecca Craighill Lancefield, 1895–1981," *Biographical Memoirs* (Washington, DC: National Academy of Sciences, 1987), 227–28.

⁵ O'Hern, "Rebecca Craighill Lancefield, Pioneer Microbiologist," 806.

⁶ Merrill W. Chase, "Rebecca C. Lancefield: Luncheon 3/6/75," American Association of Immunologists Records, Box 8, Folder 43, University of Maryland, Baltimore County.

⁷ A. R. Dochez and O. T. Avery, "Soluble Substance of Pneumococcus Origin in the Blood and Urine During Lobar Pneumonia," *Proceedings of The Society for Experimental Biology and Medicine* 14 (1917): 126–27; "The Elaboration of Specific Soluble Substance by Pneumococcus During Growth," *Journal of Experimental Medicine* 26, no. 3 (1917): 477–93; "The Elaboration of Specific Soluble Substance by Pneumococcus During Growth," *Transactions of the Association of American Physicians* 32 (1917): 281–98.

⁸ Chase, "Rebecca C. Lancefield."

⁹ It is unclear where Wollstein went to carry out her research in the summer of 1918. As an authority on Pfeiffer's bacillus (now known as *Haemophilus influenzae*), she was involved in research and clinical projects throughout the 1918 influenza pandemic. Until 1933, Pfeiffer's bacillus was considered the causative agent of the 1918 influenza pandemic. See John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (New York: Penguin, 2005), 411–12.

¹⁰ Chase, "Rebecca C. Lancefield."

believed to be the causative agent of secondary infections, such as pneumonia, puerperal fever, rheumatic fever, and wound infections, which typically followed measles and influenza. Avery and Dochez had been enlisted precisely because of their success in classifying four types of pneumococci,¹¹ as well as for their clinical understanding of the disease. The researchers sought to determine whether streptococci, like pneumococci and some other bacteria, were comprised of only one or several distinct types.

Shortly before Lancefield joined their laboratory, Dochez and Avery described their frustration with typing their samples from Texas at an early June 1918 Rockefeller conference on hemolytic streptococci. They indicated that they still did not know whether they were dealing with distinct strains, citing problems with both agglutination and mouse protection. Dochez explained to those in attendance that, “[u]p to now... we have been unable to obtain immune serum which affords any considerable degree of protection for white mice against experimental infection. We are still working along this line and it is possible that the proper combination of immune serum and test animal may be obtained.”¹²

Lancefield assisted Avery and Dochez in the laboratory with their typing problem. Within one year, the lab had classified 70 percent of the 125 samples they had collected in Texas into four distinct serological types of streptococcus. Lancefield’s role in this process was, no doubt, significant. Avery and Dochez cited her as a co-author in the resulting article, “Studies on the Biology of Streptococcus: I. Antigenic Relationships Between Strains of *Streptococcus hemolyticus*.”¹³



Rebecca and Donald Lancefield, c. 1928

Image courtesy of Rockefeller Archive Center

A slight diversion

Shortly after their results were published, funding for the Army-supported streptococcal project ceased with the war’s end, and Dochez and Avery gladly returned to their pneumococcal research. Dochez accepted a position at Johns Hopkins University, and Lancefield, no longer funded at RIMR, accompanied her husband and the Columbia zoology group to their annual summer trip to the Marine Biological Laboratory at Woods Hole, Massachusetts.¹⁴ While there, Lancefield met Morgan and was hired to work as a technician in his lab at Columbia University.¹⁵ She worked there for two years on a *Drosophila* genetics study under Charles W. Metz. Taking advantage of the access her employment at Columbia provided her, she took Morgan’s genetic course as well as the pioneering cytology course taught by notable cell biologist Edmund B. Wilson.¹⁶

When, in 1921, her husband, Donald, was offered the opportunity to teach zoology at the University of Oregon, both Lancefields made the move. For Donald, it was a homecoming to a state that his mother had entered aboard a covered wagon at the age of ten. Rebecca was also able to secure an appointment teaching bacteriology. The homecoming was short-lived, though, for, at the end of the school year, Donald accepted an offer to join Morgan’s Department of Zoology at Columbia University. The Lancefields returned to New York where Rebecca seized the opportunity to begin her doctoral training in bacteriology under Zinsser at Columbia.¹⁷

Return to streptococcus

Lancefield returned to working on streptococcus, not only at Columbia but also at RIMR. Zinsser was not fond of women in the laboratory and was quick to recommend that Rebecca find laboratory space at RIMR with Homer Swift (AAI ’20), who was beginning a new study of rheumatic fever.¹⁸ Lancefield obtained a position under Swift, an arrangement that she later recalled required her to



Hans Zinsser, ca. 1919

Image courtesy of the Center for Biological Sciences Archives, UMBC

¹¹ Dochez established a biological classification of pneumococci into specific types in 1913, and, as part of an ongoing study of the immunological classification of pneumococci, he worked with Avery through 1917 in identifying the four distinct types by identifying the specific soluble substance that confers type specificity upon the pneumococci.

¹² McCarty, “Rebecca Craighill Lancefield,” 229.

¹³ A. R. Dochez, O. T. Avery, and R. C. Lancefield, “Studies on the Biology of Streptococcus: I. Antigenic Relationships Between Strains of *Streptococcus hemolyticus*,” *Journal of Experimental Medicine* 30, no. 3 (1919): 179–213; McCarty, “Rebecca Craighill Lancefield,” 228–30.

¹⁴ O’Hern, “Rebecca Craighill Lancefield, Pioneer Microbiologist,” 806.

¹⁵ Chase, “Rebecca C. Lancefield.”

¹⁶ Chase, “Rebecca C. Lancefield”; O’Hern, “Rebecca Craighill Lancefield, Pioneer Microbiologist,” 806.

¹⁷ O’Hern, “Rebecca Craighill Lancefield, Pioneer Microbiologist,” 806.

¹⁸ Ibid.

carry “my racks of test tubes back and forth between the two labs” during these years.¹⁹

At the time, the causative agent of rheumatic fever was unknown, and Swift and Lancefield’s first study attempted to isolate the “specific soluble substance”—polysaccharides, such as those being identified on pneumococcus, or other antigens—species specific for streptococci.²⁰ When this study proved inconclusive, Swift next suspected that the α -hemolytic class of streptococcus (also called “green” or viridans streptococci) was the causative agent.²¹ Lancefield’s doctoral research consisted of testing this hypothesis. After two years of painstaking laboratory work, she had proved conclusively that the α -hemolytic streptococci were not responsible for rheumatic fever, and she had earned her Ph.D.²²

After completing her doctorate in bacteriology in 1925, Lancefield returned to her research on hemolytic streptococci at RIMR by returning to a more basic approach to understanding which classes of streptococci caused diseases in humans. Although Dochez, Avery, and she had identified four distinct serological types in 1919, there had been little research on understanding the determining chemical and biological properties of the antigens on the surface of the bacteria that were responsible for the virulence and pathogenesis of many of the now-known streptococcal infections, such as strep throat, scarlet fever, rheumatic fever, and mastitis.²³



Rockefeller Institute for Medical Research, c. 1925

Image courtesy of Rockefeller Archive Center



Pneumococcus

Image courtesy of the Centers for Disease Control and Prevention/Dr. M. S. Mitchell

Developing a classification system

Having been immersed in Avery’s methodology, Lancefield adopted many of the typing techniques she had used for typing pneumococci. She began her research by resurrecting the 125 dried streptococcal cultures collected by Dochez and Avery in Texas.²⁴ She soon began to make progress in classifying β -hemolytic streptococci through her laborious and detailed serological grouping and typing. But, the classification system that she was beginning to develop was not her ultimate objective. Instead, it was a means to her goal of identifying the antigens and determining their role in the pathogenic capability of the bacteria.²⁵

In a series of articles in 1923, Avery and Michael Heidelberger (AAI ’35, president 1946–47, 1948–49) demonstrated that type-specific antigens in pneumococcus were composed of polysaccharides. Their conclusions were verified

subsequently by other researchers, who also identified similar capsular polysaccharides on pathogenic bacteria determining type specificity. In the mid-1930s, Lancefield isolated two soluble surface antigens from streptococci. The first was type-specific for the various strains of the 1918 epidemic, and the second was species-specific, present in all of the strains taken from infected humans. Lancefield, working just down the hall from Avery, expected to find that the type-specific antigens of streptococci were also composed of complex carbohydrates.

In further experimentation, she was surprised to discover that the type-specific antigen was a protein. She identified the protein and later called it the M-protein, in reference to the growth of a matt colony when the bacteria sample is exposed to the antigen on an agar medium. She further concluded that this protein was responsible for the virulence factor of streptococci.

The species-specific antigen, however, was comprised of carbohydrates, which she called the C-carbohydrate.

¹⁹ Lawrence K. Altman, “Dr. R. C. Lancefield, Bacteriologist, Dies,” *New York Times*, 4 March 1981.

²⁰ Chase, “Rebecca C. Lancefield.”

²¹ Termed “green” because they cause oxidization of iron in hemoglobin molecules on blood agar plates.

²² Rebecca C. Lancefield, “The Immunological Relationships of *Streptococcus viridans* and Certain of Its Chemical Fractions: I. Serological Reactions Obtained with Antibacterial Sera,” *Journal of Experimental Medicine* 42, no. 3 (1925): 377–95; “The Immunological Relationships of *Streptococcus viridans* and Certain of Its Chemical Fractions: II. Serological Reactions Obtained with Antinucleoprotein Sera,” *Journal of Experimental Medicine* 42, no. 3 (1925): 397–412.

²³ McCarty, “Rebecca Craighill Lancefield,” 231.

²⁴ Chase, “Rebecca C. Lancefield.”

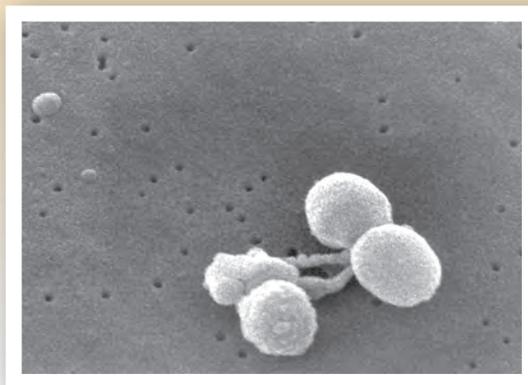
²⁵ McCarty, “Rebecca Craighill Lancefield,” 231–32.

After receiving and testing streptococcal strains from human and animal subjects across the country, she soon realized that the antigen she believed to be species-specific was actually group-specific. This differentiation in group provided the basis for her classification system and the study of streptococcal diseases. Lancefield did not publish her results as the M-protein and C-carbohydrate discoveries were made. She did, however, author a series of five articles in 1928 reporting these discoveries.²⁶

She soon began to differentiate and classify her samples, separating them into groups and specific serotypes within each group based on variations in the M-protein and C-carbohydrate. Initially, she designated group A for highly virulent streptococcal infections in humans and group B largely for bovine streptococcal infections.²⁷ By 1940, Lancefield and other researchers were refining the classification system to the extent that Lancefield had defined, or been consulted about, groups A through H and K (later dropped), L, and M.²⁸

Research after classification

Through her careful studies of group A streptococci, she classified over 50 types and revealed that the M-protein played a central role in streptococcal infections by inhibiting the phagocytosis of white blood cells. She also discovered that a single serotype could cause a variety of streptococcal diseases and that the M-protein varied across serotypes, a conclusion revealing that immunity from one type of streptococcal infection does not prevent infection by streptococcus of another serotype. This latter discovery explained why streptococcal infections, such



Streptococcus pneumoniae

Image courtesy of the Centers for Disease Control and Prevention/ Dr. Richard Facklam; Photo: Janice Haney Carr

as strep throat and rheumatic fever, are so often recurring. She also identified two new surface proteins on group A streptococci: T-antigen in 1940,²⁹ which she later determined, in 1957, meant that the new antigen did not contribute to virulence, and R-antigen.³⁰

Lancefield later turned her attention to group B streptococci—bacteria once thought to infect only bovine but soon discovered to be responsible for neonatal pneumonia and meningitis. Lancefield found that

streptococci of this group did not contain the M-protein; instead, she found that their virulence was determined by surface polysaccharides. Her research was an important first step in preventing the life-threatening diseases in newborns caused by group B streptococci.³¹

Career at Rockefeller

For nearly six decades, Mrs. L., as she became affectionately known to her colleagues, left her mark on RIMR and on immunology. During the Second World War, she served on the Commission on Streptococcal and Staphylococcal Diseases of the Armed Forces Epidemiological Board, and her willingness to answer queries and type streptococcal samples from around the country, and later from around the world, earned her laboratory at RIMR the nickname, “the Scotland Yard of streptococcal mysteries.”³² After the war, in 1946, she was promoted to an associate member at RIMR and became a full member and professor in 1958.

Lancefield’s years at Rockefeller not only allowed her to work under such early luminaries in the field as Avery, Dochez, and Swift, but they also afforded her the

²⁶ Rebecca Lancefield, “The Antigenic Complex of *Streptococcus haemolyticus*. I. Demonstration of a Type-Specific Substance in Extracts of *Streptococcus haemolyticus*,” *Journal of Experimental Medicine* 47 (1928): 91–103; “II. Chemical and Immunological Properties of the Protein Fractions,” 469–80; “III. Chemical and Immunological Properties of the Species-Specific Substance,” 481–91; “IV. Anaphylaxis with Two Non-Type-Specific Fractions,” 843–55; “V. Anaphylaxis with the Type-Specific Substance,” 857–75; Rebecca Lancefield and E. W. Todd, “Variants of Hemolytic Streptococci; Their Relation to Type-Specific Substance, Virulence, and Toxin,” *Journal of Experimental Medicine* 48, no. 6 (1928): 751–67; Rebecca Lancefield and E. W. Todd, “Antigenic Differences Between Matt Hemolytic Streptococci and Their Glossy Variants,” *Journal of Experimental Medicine* 48, no. 6 (1928): 769–90.

²⁷ Rebecca Lancefield, “A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci,” *Journal of Experimental Medicine* 57, no. 4 (1933): 571–95; Rebecca Lancefield, “A Serological Differentiation of Specific Types of Bovine Hemolytic Streptococci,” *Journal of Experimental Medicine* 59, no. 4 (1934): 441–58; McCarty, “Rebecca Craighill Lancefield,” 233–34.

²⁸ O’Hern, “Rebecca Craighill Lancefield, Pioneer Microbiologist,” 809.

²⁹ Rebecca Lancefield, “Type-Specific Antigens, M and T, of Matt and Glossy Variants of Group A Hemolytic Streptococci,” *Journal of Experimental Medicine* 71, no. 4 (1940): 521–37.

³⁰ Rebecca Lancefield, “Differentiation of Group A Streptococci with a Common R Antigen into Three Serological Types, with Special Reference to the Bactericidal Test,” *Journal of Experimental Medicine* 106, no. 4 (1957): 525–44.

³¹ McCarty, “Rebecca Craighill Lancefield,” 233.

³² Schwartz, “Mrs. L.”

opportunity to collaborate with and influence subsequent generations of immunologists: she was a long-time colleague and collaborator of Maclyn McCarty (AAI '47), who replaced Swift upon his retirement, and she served as a mentor to Emil Gotschlich (AAI '69).³³ Both McCarty and Gotschlich were recipients of Lasker Awards.³⁴ In 1965, Lancefield became professor emeritus but continued to work in her old laboratory until she suffered a broken hip in a November 1980 fall. She died on March 3, 1981, at the age of 86.³⁵

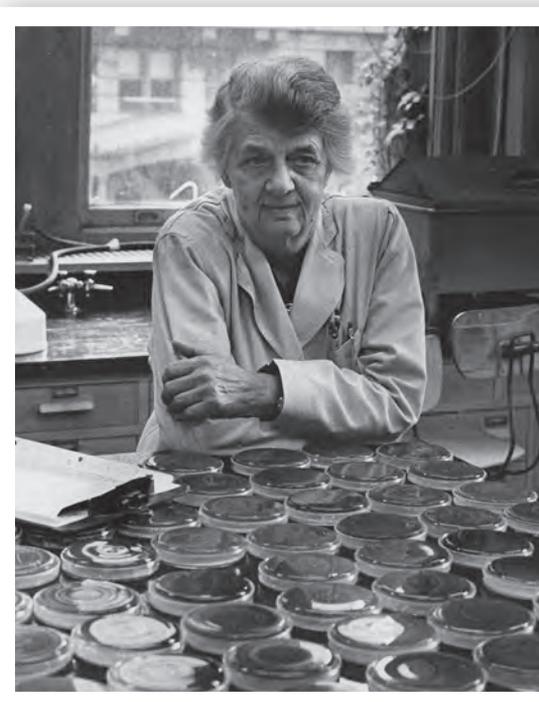
Legacy

Toward the end of her career, Lancefield received numerous honors and awards thought by many to be long overdue.³⁶ She was elected to the National Academy of Sciences (1970), which, by that time, had elected only ten women, and was awarded the T. Duckett Jones Memorial Award of the Whitney Foundation (1960), the American Heart Association Achievement Award (1964), the New York Academy of Medicine Medal (1973), and a Doctor of Science (honoris causa; 1973), the highest recognition from Rockefeller.³⁷ Perhaps the most



Rebecca Lancefield accepting the T. Duckett Jones Memorial Award; Maclyn McCarty (right), Walter Bauer (left), c. 1960

Image courtesy of the Smithsonian Institution Archive



Rebecca Lancefield in her laboratory

Image courtesy of Rockefeller Archive Center

significant honor bestowed upon her was the decision of both the national and international organizations devoted to the study of streptococcus to adopt the name, “The Lancefield Society,” in 1972 and 1977, respectively.³⁸

Lancefield was an internationally renowned research scientist, but she was also a devoted wife and mother. (She and Donald had one daughter, Jane.) Her success in balancing career and family was rare among female immunologists in the first half of the twentieth century, but she seems not to have wanted emphasis to fall on her role as a pioneering woman in science. According to a colleague, she did not relish “honors that recognized her as the ‘first woman’ to do this or that and preferred those that came without reference to her sex.”³⁹

Far more satisfying for her, one imagines, would be Maclyn McCarty’s tribute, crediting her as “the scientist most responsible for the well-organized state of our present knowledge of streptococci.”⁴⁰

³³ “Emil C. Gotschlich,” Faculty, Rockefeller University, <http://www.rockefeller.edu/research/faculty/labheads/EmilGotschlich>.

³⁴ Emil Gotschlich was awarded the 1978 Albert Lasker Clinical Medical Research Award, and Maclyn McCarty received the 1994 Albert Lasker Award for Special Achievement in Medical Science.

³⁵ McCarty, “Rebecca Craighill Lancefield,” 233.

³⁶ *Ibid.*, 238.

³⁷ *Ibid.*; O’Hern, “Rebecca Craighill Lancefield, Pioneer Microbiologist,” 810.

³⁸ Schwartz, “Mrs. L.”

³⁹ McCarty, “Rebecca Craighill Lancefield,” 240.

⁴⁰ Altman, “Dr. R. C. Lancefield, Bacteriologist, Dies.” *New York Times*.

From the Archives

What's old is new again: Early editors of *The JI* act to address perennial challenges in the peer-review and editing process

By John Emrich
and Bryan Peery

The initial challenges of financing and operating *The Journal of Immunology* (*The JI*) are well documented in the surviving records from the first two decades of the journal's history. Unfortunately, those records shed far less light on the inner workings of *The JI*. Details concerning such important issues as the responsibilities of the editorial staff, the manuscript submission procedure, and the peer-review process remain less than clear.

What is known is that when *The JI* was founded in 1916, AAI Council elected an editorial staff consisting of an editor, a board of editors, and an advisory board. The editorial process was overseen by Editor Arthur F. Coca (AAI '16), who managed the journal single-handedly from its founding until 1925 when a second editor, John C. Torrey (AAI '20), was named to help alleviate the strain of a growing workload. The members of the board of editors—usually around 30 immunologists from the United States and the United Kingdom—were responsible for reviewing and editing manuscripts. The advisory board was primarily of older, prominent scientists who had little to no editorial function but served to advise and lend prestige to the nascent journal.

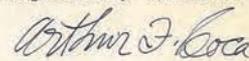
MINUTES OF THE MEETING
OF THE EDITORIAL BOARD OF THE
JOURNAL OF IMMUNOLOGY
March 24th, 1937

The first meeting of the Editorial Board of the Journal of Immunology was held in the Hotel Drake in Chicago at luncheon, March 24, 1937. Present were Sanford B. Hooker, presiding, O. T. Avery, Francis G. Blake, Jacques Bronfenbrenner, Donald T. Fraser, Arthur P. Locke, Carl Ten Broeck, A. B. Wadsworth, A. F. Coca, Paul R. Cannon and the following: Philip Levine, Leo Loeb, Kenneth Goodner, Frank Maltaner, all of whom had acted as referees for certain special papers submitted to the Journal. Present as guest of honor was also Ludvig Hektoen, who offered numerous helpful suggestions out of his long editorial experience.

There was an extended discussion of the question whether authors of rejected papers should be informed as to the reason for the rejection. It was the majority opinion that as a rule the reasons for the rejection, as stated by the referees or associate editors, should not be given verbatim to the authors.

There was considerable difference of opinion as to whether papers should be edited for clearness of expression. Examples of such editorial revisions were shown to those present. It was agreed that the thorough editorial work of Doctors Hooker, Berry and Blake, illustrated in the submitted samples, is of great value to the Journal and its readers, and of educational value to the authors. No formal action was taken on this question.

Respectfully submitted



Arthur F. Coca
Editor-in-Chief

From time to time, the AAI Office of History and Archives will publish an archival document related to the history of the association. Each document will be accompanied by a brief introductory note providing some historical context. Readers interested in learning more about a particular document will find more extensive information in annotations provided in the History section of the AAI website.

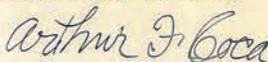
MINUTES OF THE MEETING
OF THE EDITORIAL BOARD OF THE
JOURNAL OF IMMUNOLOGY
December 28th, 1937

The second meeting of the Editorial Board of the Journal of Immunology was held in the Hotel Mayflower at dinner, December 28, 1937. Present were Oswald T. Avery, George P. Berry, Jacques Bronfenbrenner, Arthur F. Coca, Alphonse R. Dochez, Michael Heidelberger, Sanford B. Hooker, Earl B. McKinley, Stuart Mudd, Thomas M. Rivers, Carl Ten Broeck and Alexander S. Wiener, and also Barnett Cohen, N. Paul Hudson and C.-E. A. Winslow of the Journal of Bacteriology.

The chief topic of discussion was the same as that at the first meeting. Dr. Coca reported that the editors, especially the associates, have been unnecessarily burdened with the labor of correcting - often practically rewriting - papers which had been carelessly composed and apparently not given any revision in the institutions in which they had originated. Examples of corrected manuscripts were passed around.

Most of those present, including Drs. Winslow and Cohen, expressed themselves in favor of rigorous editing of the English form as well as of the factual content of accepted papers and approved the suggestion that our members and also institutions from which papers are likely to be received be requested to exert all reasonable influence to have papers carefully revised at their source in accordance with our editorial practice.

Respectfully submitted



Arthur F. Coca
Editor-in-Chief

The structure of the editorial staff remained unchanged for almost two decades, even though its workload nearly doubled in that span of time. In its first five years, *The JI* was published every two months, averaging approximately 37 scientific articles and 525 pages per year. Between 1929 and 1934, however, the journal was published monthly and averaged approximately 79 scientific articles and 1,035 pages per year. Not only did the number of submissions rise steeply, they also became increasingly specialized and diversified, reflecting the growth of the burgeoning field of immunology. The editorial staff, as initially established in 1916, was no longer able to review and edit the influx of new submissions efficiently and effectively.

On Friday, December 27, 1935, a special meeting of the AAI Council convened in New York City to discuss the restructuring of the editorial staff and peer-review process of *The JI*. A select committee, comprised of Drs. Thomas M. Rivers (AAI '21, president 1933-34), chairman; Stanhope Bayne-Jones (AAI '17, president 1930-31); and Arthur F. Coca presented a "plan of reorganization."

Continued on next page

*Historical documents courtesy
of The American Association of
Immunologists Archive, Bethesda, MD*

The committee proposed restructuring the editorial staff to more efficiently review and edit the greater volume and breadth of manuscripts submitted to *The JI*. Under the new plan, the journal would be managed by an editorial staff consisting of “an Editor in Chief and at least three Associate Editors, with the advice of a Board of Editors,” whose members would now be required to reside in North America. The proposal also specified a new process for handling, evaluating, and editing manuscripts. The following is the language used to specify what was to become the first official peer-review process approved by the Council:

1. All papers to be sent to the Editor in Chief.
2. Editor in Chief to send each paper to a specialist on the Editorial Board, or elsewhere if necessary, for acceptance or rejection. If accepted, the specialist should comment on changes necessary.
3. Paper is then sent back to the Editor in Chief.
4. From the Editor in Chief, the paper goes to the proper Associate Editor for careful editing and approval.
5. The paper is returned to the Editor in Chief.
6. The Editor in Chief returns the paper to the author with all the changes made or suggested by the Associate Editor.
7. Paper comes back from the author to the Editor in Chief for final approval, who then sends it to the publisher and handles the proof, etc.*

The Council approved the reorganization and peer-review process at this special December 1935 meeting, voting also to limit papers to 20 printed pages; authors would be required to pay for any pages in excess of the limit.

After accepting the reorganization plan, the Council sent letters of thanks to the 25 outgoing members of the board of editors and to the advisory board for their service. The new “editorial board”—the term adopted by Council to refer to the entire editorial staff—would consist of Coca as the editor-in-chief, three associate editors, and a 21-member board of editors. The new staff began its work in January 1936. Of the 25 editorial staff members, 17 had been or would become president of AAI.

The chief topic of discussion was the same as that at the first meeting. Dr. Coca reported that the editors, especially the associates, have been unnecessarily burdened with the labor of correcting—often practically rewriting—papers which had been carelessly composed and apparently not given any revision in the institutions in which they had originated. Examples of corrected manuscripts were passed around.

The first meeting of the new editorial board occurred on March 24, 1937, during the twenty-fourth annual meeting of AAI in Chicago, Illinois. Discussions at the meeting focused on the challenges in handling rejected manuscripts and determining the amount of revising and editing necessary to prepare papers for publication. Unable to resolve these concerns at a single meeting, the board met for a second time on December 28, 1937, in New York City specifically to address the burden of “correcting—often practically rewriting—papers.” Evidently, these problems were too big to resolve in 1937, as they continue to cause sleepless nights for editors and authors alike. We present the minutes of the first two editorial board meetings here; an annotated version will be available on the AAI website at www.aai.org/about/history. ■

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

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

* Procedures as recorded in the minutes of the special meeting of the AAI Council on December 27, 1935.

A Legacy of Advocacy Is Born as AAI Confronts McCarthyism

by Bryan Peery and John Emrich

Today, across-the-board cuts in federal funding for scientific research threaten to drive leading scientists overseas and deter the next generation from entering scientific professions. Sixty years ago, scientists had similar concerns for their own funding, albeit for very different reasons.

Although federal spending was on the rise in the decades immediately following the Second World War, it was also the height of the Second Red Scare associated with Senator Joseph McCarthy (R-WI), and scientists faced the possibility of having their individual funding withheld on the basis of mere rumor or innuendo about their past political associations.

In this political climate, scientists increasingly turned to their professional societies to defend their interests before policy makers. The leadership of the American Association of Immunologists (AAI) chose to address the crisis. Rather than limit themselves to defending individual members, AAI leaders spoke out for all victims of the unjust policy, plunging headlong into the complicated waters of public affairs for the first time. Not only did they draft a resolution protesting the policy of discriminating against researchers based on personal politics, but they also worked with representatives of other scientific organizations to ensure that scientists' concerns were heard by policy makers. The organized protest proved effective, and the government policies regarding unclassified research grants were changed. This first overt engagement in public policy by AAI demonstrated the importance of collective political action and laid the groundwork for the next 60 years of advocacy on behalf of immunologists.

A Call to Political Action

Following sessions on poliomyelitis and complement, attendees at the 1954 AAI annual meeting turned their attention from science to politics as they convened



Members of the House Un-American Activities Committee outside of Chairman J. Parnell Thomas's home (l-r): Rep. Richard B. Vail, Rep. Thomas, Rep. John McDowell, Robert Stripling (chief counsel), and Rep. Richard M. Nixon

New York World-Telegram and the Sun Newspaper Photograph Collection, Library of Congress

for the business meeting late in the afternoon on Tuesday, April 13. Rumors that the U.S. Public Health Service (USPHS), which administered National Institutes of Health (NIH) grants, was blacklisting scientists on political grounds had circulated among attendees during the first two days of the Federation of American Societies for Experimental Biology (FASEB) meeting. Disturbed by these rumors, Michael Heidelberger (AAI '35, president 1946–47, 1948–49) brought the matter to the floor of the business meeting. A firm believer that scientists could not afford to stay aloof from politics in the

postwar era, Heidelberger had used the occasions of his two AAI president's addresses to call for openness and international cooperation in science and to challenge AAI members to become politically engaged.¹ Now he called upon AAI to issue a formal protest of the alleged USPHS policy.

At the suggestion of Albert Sabin (AAI '46), a committee comprised of Heidelberger, Thomas P. Magill (AAI '37, president 1953–54), and Morris Scherago (AAI '48) drafted a resolution in April 1954 protesting the blacklisting and mailed it to AAI members for a vote. The resolution recognized the necessity of secrecy and thorough background checks in classified research but argued that such measures were unnecessary in unclassified areas. It "earnestly urge[d]" that unclassified research funds "be allocated solely on the basis of scientific merit of the proposals and for the competence of the investigators involved, and that no funds be denied because of the investigator's political associations or beliefs."²

1. Michael Heidelberger, "Science, Freedom and Peace," *Federation Proceedings* 6 (1947): 484–85; *Ibid.*, "Ivory Pawn in the Ivory Tower," *Federation Proceedings* 8 (1949): 579–80.

2. Resolution and mail ballot attached to the minutes of the AAI Business Meeting, April 13, 1954, AAI Archive, Bethesda, MD [hereafter AAI-Bethesda].

McCarthyism and the NIH Blacklists

The rumors about the USPHS were new in 1954, but the practice of blacklisting individuals whose politics were deemed subversive was not. Shortly after the end of the Second World War, anti-communist sentiment quickly grew in the United States (see “The Roots of McCarthyism,” p. 43). The fear of communist subversion was so pervasive by March 1947 that President Truman issued Executive Order 9835, which established a federal loyalty program and subjected all current and future federal employees to loyalty tests and reviews. If Federal Bureau of Investigation (FBI) records or testimony from anonymous informants provided “reasonable grounds” to suspect an employee of affiliating with a group deemed by the attorney general to be subversive, the employee could be summarily dismissed. Although employees were entitled to a hearing before the Loyalty Review Board, they were not provided the names of their accusers, much less afforded the opportunity to confront them in court.

The House Un-American Activities Committee (HUAC) extended the search for communists beyond the federal workforce and perpetuated the notion that communists in every sector of American society threatened the nation from within. HUAC captured headlines with the well-known investigations of the Hollywood Ten in 1947 and Alger Hiss in 1948. Other HUAC cases, such as that of physicist Edward U. Condon in 1948, may be less familiar to us today but were nonetheless significant at the time. In fact, the AAI Council first spoke out against the tactics associated with McCarthyism when it issued a resolution at the 1948 AAI annual meeting condemning HUAC for its handling of the Condon case (see “Protesting the Politicization of Science,” p. 45).³

American anxiety over communism increased dramatically in response to global and domestic developments of the late 1940s and early 1950s. The Soviets carried out their first successful atomic bomb test in August 1949, and Mao Zedong proclaimed the establishment of the communist People’s Republic of China two months later. On February 2, 1950, Klaus Fuchs was arrested for espionage, sparking the investigation that, months later, resulted in the arrest of Julius and Ethel Rosenberg. One week after Fuchs’s arrest, Senator Joseph McCarthy rose to national



Oveta Culp Hobby speaking at the dedication of the NIH Clinical Center, 1953
Images from the History of Medicine, National Library of Medicine

prominence when he delivered a speech in Wheeling, West Virginia, dramatically claiming to have in his hand a list of subversives in the State Department.

It was against this backdrop that the USPHS changed its procedures for screening NIH grant applications in June 1952. The change had been implemented quietly and was known to members of AAI and other FASEB societies only as an unverified rumor when they met in early April 1954. Confirmation came only after the FASEB meeting when the American Society of Biological Chemists issued a resolution calling upon the National Academy of Sciences (NAS) to investigate the rumors.⁴

Oveta Culp Hobby, secretary of the U.S. Department of Health, Education, and Welfare,⁵ responded to the inquiry with the following statement on April 28:

We do not require security or loyalty investigations in connection with the award of research grants. When, however, information of a substantial nature reflecting on the loyalty of an individual is brought to our attention, it becomes our duty to give it more serious consideration. In those instances where it is established to the satisfaction of this Department that the individual has engaged or is engaging in subversive activities or that there is serious question of his loyalty to the United States, it is the practice of the Department to deny support.

According to Hobby, more than 2,000 NIH grants had been awarded to 14,000 scientists in each of the

Continued page 60

3. Minutes of the AAI Council Meeting, March 15, 1948, AAI-Bethesda.

4. The American Society of Biological Chemists (ASBC) changed its name to the American Society for Biochemistry and Molecular Biology in 1987. A copy of the ASBC resolution is attached to a memorandum from Alwin M. Pappenheimer and F. Sargent Cheever to AAI Councillors, July 13, 1954, Box 1, Folder 2, Councillors’ Correspondence (Chase), The American Association of Immunologists Collection, University of Maryland, Baltimore County [hereafter AAI-UMBC].

5. Now the U.S. Department of Health and Human Services.

The Roots of McCarthyism: Communism and Anti-Communism in America

Since the Alien and Sedition Acts of 1798, anti-radicalism and fear of internal subversion have been recurring themes in American politics. It is therefore no surprise that when the Communist Party USA (CPUSA) was founded in 1919, the party's revolutionary rhetoric, and the fact that the overwhelming majority of its members were recent immigrants from Southern and Eastern Europe, immediately aroused suspicion. Following a series of highly publicized bombings by subversive political elements, Attorney General A. Mitchell Palmer, with the backing of Congress and widespread public support, launched a series of raids in cities across the country in December 1919 and January 1920 that rounded up thousands of individuals suspected of being communists. Hundreds of aliens were deported during what became known as the Red Scare, and the CPUSA was driven underground—its membership falling below 10,000.¹

During the turbulent times of the Great Depression, the CPUSA enjoyed a period of relative success in American politics. Communists worked with progressive groups in the 1930s and attracted new party members by playing a leading role in the social struggles of the day. By the mid-1930s, Americans who championed labor rights, organized the unemployed, fought evictions of farmers and the working poor, promoted civil rights, or called for the U.S. government to take a stand against growing European fascism by intervening in the Spanish Civil War (1936–39) necessarily found themselves working alongside CPUSA members, whether they officially joined the party or were simply “fellow travelers.” For their part, the communists, who once condemned both major American political parties, openly supported President Franklin D. Roosevelt's trade unionization efforts and publicly acknowledged the Democrats as the lesser of two evils by the 1936 presidential election.

Following the signing of the Nazi-Soviet pact and the Russian invasion of Poland in 1939, the CPUSA quickly lost much of the goodwill it had engendered during the Great Depression. The change in policy confirmed suspicions that the party was under direct control of the Soviet government, and, thereafter, the reputation of the CPUSA was tied to that of the Soviet Union.

When Hitler invaded Russia in June 1941, the Roosevelt administration and its supporters, who were, by then, committed to aiding the Allies, actively worked to improve Americans' impressions of the Soviet Union. This U.S.-Soviet cooperation flourished briefly after the United States entered the Second World War, but the relationship quickly soured with the war's end, as both the U.S. and Soviet governments sought to control the post-war world order.

While many liberals, however reluctantly, learned to work with communists during the Great Depression and the Second World War, conservatives (most, but not all of them, were Republicans) never ceased their criticism of communism as un-American. Many critics of President Roosevelt's policies charged that the president was a socialist, and a vocal minority even suggested that his administration was infiltrated with communists who were loyal to the Soviet Union. These charges failed to stick during the 1930s or early 1940s, but Republicans had far more success in portraying the Democratic Party as “soft” on communism by the end of the decade, as they blamed Roosevelt and his successor, President Harry S. Truman, for the “fall” of Eastern Europe and China to communism.

No sector of society was safe from accusations of disloyalty. Leaders of all fields, including science, soon recognized that even their past political affiliations, if only slightly outside of the mainstream, could cost them their careers.

President Truman attempted to seize the domestic communism issue from the Republicans by signing Executive Order 9835 and instituting the federal loyalty program in March 1947, but the Republican-controlled House Un-American Activities Committee conducted high-profile investigations into communist

subversion and further stirred anti-communist sentiment. By the end of the 1940s, the foundation for the systematic persecution of those whose loyalty was called into question had been put into place. Once the federal government implemented the Truman loyalty program and legitimized the practice of screening employees based on their political beliefs and affiliations, similar policies were rapidly adopted by state and local governments as well as private organizations, including universities.²

No sector of society was safe from accusations of disloyalty. Leaders of all fields, including science, soon recognized that even their past political affiliations, if only slightly outside of the mainstream, could cost them their careers.

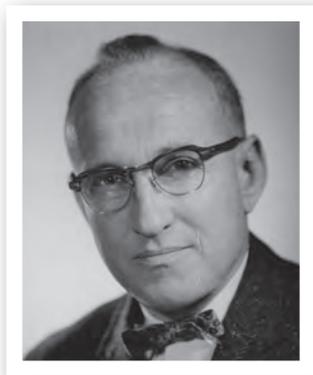
1. This brief overview of communism and anti-communism in the United States is based on Richard M. Fried, *Nightmare in Red: The McCarthy Era in Perspective* (New York: Oxford University Press, 1990), and Ellen Schrecker, *The Age of McCarthyism: A Brief History with Documents*, 2nd ed. (Boston: Bedford/St. Martin's, 2002).

2. Ellen Schrecker, *No Ivory Tower: McCarthyism and the Universities* (New York: Oxford University Press, 1986).

two years since the policy change, and fewer than 30 individuals had been denied funding on the basis of the policy.⁶

Elvin A. Kabat versus the NIH

Some of those individuals whose grant applications were rejected under the USPHS policy were likely unaware that they had been blacklisted, and many of those who did suspect that they had been denied funding for political reasons undoubtedly kept quiet to save their careers. Nevertheless, AAI leaders were aware of at least three individuals who were on the USPHS blacklists: the names, “Pauling,” “Kabat,” and “Peters,” are handwritten in the corner of one of AAI Councillor Merrill Chase’s (AAI ’38, president 1956–57) letters regarding the resolution of protest.⁷



Elvin A. Kabat, ca. 1965
The American Association of Immunologists Collection, Center for Biological Sciences Archives, UMBC

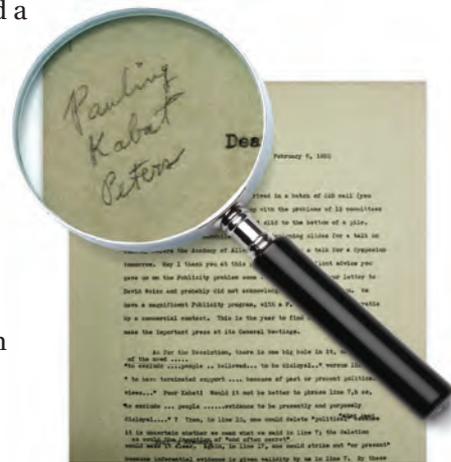
Both Nobel laureate Linus Pauling and distinguished Yale biomedical research scientist John P. Peters brought public attention to their cases in 1954 and 1955,⁸ but there can be little doubt that when Heidelberger called upon AAI to act on the matter in April 1954, it was the plight of his former student, colleague at the Columbia University College of Physicians and Surgeons (P&S), and friend, Elvin A. Kabat (AAI ’43, president 1965–66), that weighed heavily on his mind. Heidelberger knew that Kabat had been under investigation by the FBI for his alleged communist affiliations for the past few years, and he dismissed these accusations as “manifestly absurd and of cruel potential damage to the career of one of our most promising and brilliant young scientists.”⁹

In 1953, Kabat had applied to have an NIH grant renewed, only to be informed that his application “falls

in the group of applications for which grants cannot be made.”¹⁰ His other existing NIH grants were promptly terminated. USPHS officials offered clarification during a visit with Houston Merritt, chair of the Department of Neurology at P&S where Kabat was conducting the NIH-sponsored research. They informed Merritt that the grant application was rejected because of Kabat’s past political associations but would be reconsidered if resubmitted without his name. Kabat refused to agree to this arrangement and instead imposed a boycott on USPHS. No one receiving USPHS funds would work in his laboratory until the blacklist was lifted.¹¹

Kabat first encountered McCarthyism in 1947, when he began working as a part-time consultant at the Bronx Veterans Administration

Hospital, a position that required a loyalty and security investigation in accordance with Truman’s Executive Order 9835. During the investigation an anonymous informant, whom Kabat later identified as chemist and Nobel laureate James Batcheller Sumner, told the FBI that Kabat had been a communist in 1937–38, the year that Kabat and Sumner were research fellows together in Uppsala, Sweden.¹² Kabat was dismissed by the Veterans Administration in light of this information, but he appealed the decision to the Loyalty Review Board and was reinstated as a consultant.¹³



Letter from AAI Councillor Merrill W. Chase to Secretary-Treasurer F. Sargent Cheever, February 6, 1955, with the names Pauling, Kabat, and Peters inscribed at upper left
The American Association of Immunologists Collection, Center for Biological Sciences Archives, UMBC

Continued page 62

6. The backstory behind the Hobby statement is explained by A. M. Pappenheimer in a letter to John H. Dingle dated October 29, 1954. A copy of the statement is attached to the letter. Box 1, Folder 1, Councillors’ Correspondence (Dingle), AAI-UMBC.

7. M. W. Chase to F. S. Cheever, February 6, 1955, Box 1, Folder 2, Councillors’ Correspondence (Chase), AAI-UMBC.

8. On the Pauling case, see Scientists’ Committee on Loyalty and Security, “Loyalty and U.S. Public Health Service Grants,” *Bulletin of Atomic Scientists* 11, no. 5 (1955): 197. On Peters, see Jessica Wang, *American Science in an Age of Anxiety: Scientists, Anticommunism, and the Cold War* (Chapel Hill: University of North Carolina Press, 1999), 286, and Theodore B. Schwartz, “Two against McCarthyism: Me and John P. Peters,” *Perspectives in Biology and Medicine* 44, no. 3 (2001): 438–45.

9. M. Heidelberger to Loyalty Review Board, Bronx Veterans Administration Hospital, February 21, 1949, Michael Heidelberger Papers, MS C 245, Box 3, MH51A5, National Library of Medicine, Bethesda, MD [hereafter MH-NLM].

10. Elvin A. Kabat, “Getting Started 50 Years Ago—Experiences, Perspectives, and Problems of the First 21 Years,” *Annual Review of Immunology* 1 (1983): 1–32, quote from 31.

11. *Ibid.*, 31.

12. *Ibid.*, 27.

13. *Ibid.*, 28.

Protesting the Politicization of Science

AAI Decries HUAC Treatment of Edward U. Condon

“Our scientists, it seems, are well schooled in their specialties but not in the history of Communist tactics and designs,” wrote staunch conservative Rep. J. Parnell Thomas (R-NJ) in the weekly magazine *Liberty* in June 1947, a few months after he was appointed chairman of the House Un-American Activities Committee (HUAC). “They have a weakness for attending meetings, signing petitions, sponsoring committees, and joining organizations labeled ‘liberal’ or ‘progressive’ but which are actually Communist fronts.”¹

Thomas’s criticism was aimed at those scientists who actively resisted the secrecy and isolationism that he and many other politicians sought to impose on scientific research in the United States after the Second World War. One scientist, in particular, became the object of Thomas’s criticism—well-respected nuclear physicist and pioneer in quantum mechanics Edward U. Condon. On March 1, 1948, Condon, then the director of the National Bureau of Standards, became the subject of the first high-profile loyalty case involving a scientist when a HUAC subcommittee chaired by Thomas called him “one of the weakest links in our atomic security.”²

During the Second World War, Condon had served briefly as associate director of Los Alamos under J. Robert Oppenheimer but resigned after only six weeks in protest of some of the more stringent Manhattan Project security practices.³ He had accepted the need for security measures, such as fingerprinting and pre-hire background interviews, but protested others, especially the compartmentalization policies that prevented researchers from knowing what research teams working on other aspects of the same project were doing. Despite his disagreements with security officers at Los Alamos in 1943, Condon’s security clearance remained intact, and he continued to serve as a consultant on the Manhattan Project until 1945, when he was confirmed, without dissent, as director of the National Bureau of Standards by the Senate.

After the war, however, Condon’s aversion to secrecy and his support for international scientific cooperation appear to have been enough to attract the attention of Thomas and his HUAC colleagues. In terms of specific charges against Condon, the subcommittee report made much of his membership in the American-Soviet Science Society, an organization formed during the war to foster scientific cooperation between the two allied nations, but which was now deemed a communist front by HUAC.

AAI and four of the other five Federation of American Societies for Experimental Biology member societies were

among the first scientific organizations to protest the mistreatment of Condon.⁴ Meeting in Atlantic City, New Jersey, on March 15, 1948, the AAI Council approved a strongly worded resolution declaring that it “deplores the accusations made against American scientists” by the HUAC subcommittee. “At a time when there is increasing need for scientists of the highest caliber in the Government service,” the resolution continued, “we regret the use of methods which lack the elements of fair play inherent in the American concept of democracy and resemble more the very tactics of those foes of democracy the Committee is striving to guard against.” The resolution was sent to HUAC, and copies were mailed to AAI members so that they might forward them to their members of Congress.⁵

In the short-term, Condon and his supporters were victorious. In addition to the outpouring of support he received from scientists, he was also publicly defended by President Truman, who invoked executive privilege and refused to hand over any files related to the loyalty program to members of Congress. Without access to the files, Thomas and HUAC dropped the investigation. In July 1948, the Atomic Energy Commission renewed Condon’s security clearance, and the case faded from the headlines.

Although no longer chaired by Thomas, who resigned his seat in December 1949, HUAC subpoenaed Condon in August 1952. No new evidence was presented in the hearing, but the committee’s report nevertheless declared that Condon was unsuitable for any position that required a security clearance. As individual agencies, not Congress, granted security clearances, the report was nonbinding. When Condon, in his capacity as director of research and development at the Corning Glass Company, applied for a new clearance to work on a contract with the U.S. Navy in June 1954, he initially received it. In October, however, the secretary of the Navy revoked the clearance and ordered a second security review after the Republicans used the Condon case as political fodder in the mid-term election. Fed up with having his loyalty questioned repeatedly, Condon retired from Corning and sought an academic appointment. Yet even in academia, the HUAC accusations impeded his search for permanent employment, and several universities withdrew their offers before he settled in at the University of Colorado at Boulder.⁶

1. J. Parnell Thomas, “Reds in Our Atom-Bomb Plants,” *Liberty*, June 12, 1947, 15, 90–93, quote from 90.

2. Quoted in Jessica Wang, *American Science in an Age of Anxiety: Scientists, Anticommunism, and the Cold War* (Chapel Hill: University of North Carolina Press, 1999), 132.

3. *Ibid.*, 133.

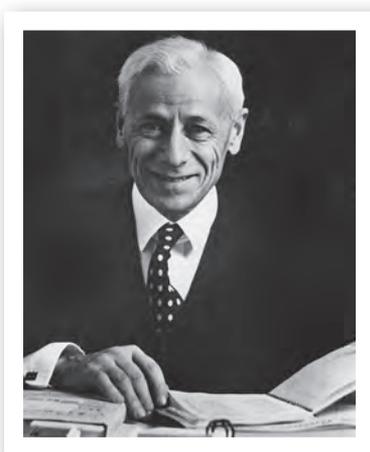
4. “Biologists Assail Thomas Committee,” *New York Times*, March 20, 1948, 15.

5. Minutes of the AAI Council, March 15, 1948, AAI Archive, Bethesda, MD.

6. For an overview of the Condon case, see Wang, *American Science in an Age of Anxiety*, 130–45; Wang, “Science, Security, and the Cold War: The Case of E. U. Condon,” *Isis* 83, no. 2 (1992): 238–69; and Robert K. Carr, *The House Committee on Un-American Activities, 1945–1950* (Ithaca, NY: Cornell University Press, 1952): 131–53, 384–90.

When it first dismissed Kabat, the Veterans Administration notified the local passport office of its findings, and Kabat's passport was revoked. Although Kabat won his appeal before the Loyalty Review Board, his passport was not returned, and he was unable to attend the First International Congress of Allergists in Zurich, at which he was scheduled to deliver a plenary lecture in 1951.¹⁴ That year, President Truman responded to increased political pressure to get tougher on communism by changing the standard for dismissal from government positions from "reasonable grounds" to suspect disloyalty to "reasonable doubt" of loyalty, shifting the burden of proof from agency loyalty boards to those individuals suspected of being disloyal.¹⁵ Rather than endure another round of loyalty hearings, Kabat resigned his position at the VA hospital.¹⁶

Although never a Communist Party member, Kabat, like many politically progressive Americans at the time, held the Soviet Union in high esteem during the 1930s (see "The Roots of McCarthyism," p. 43). Reflecting on his political leanings during these tumultuous years in 1983, Kabat recalled how the economic hardships that his family endured during the Great Depression had radicalized him and how he had admired the Soviet stand against fascism during the Spanish Civil War (1936–39), when the United States, Britain, and France attempted to remain neutral.¹⁷ He had even traveled to Leningrad and Moscow in the summer of 1937,



Michael Heidelberger, ca. 1953

Lasker Foundation

before his fellowship year in Uppsala, and then to Spain the following summer, despite the fact that his U.S. passport did not permit him to do so.¹⁸ When Stalin agreed to the Nazi-Soviet pact in 1939, Kabat grew disillusioned with the Soviet Union and communism, later writing that the pact, along with the subsequent Soviet invasions of Poland and Finland, "shook me and I began to worry about my political views."¹⁹ But, in 1941, after Germany invaded Russia, "the doubts generated by the Nazi-Soviet pact were stilled," and Kabat helped establish a Russian war relief group at the Columbia University Medical Center.²⁰ Even in the turbulent 1930s, these activities placed Kabat on the far left of the political spectrum; they were not, however, seen as sinister until the late 1940s.

Kabat's prominence prepared him to survive the ordeal better than could other, less distinguished scientists. Immediately after losing his NIH grants, Kabat secured funding from the Office of Naval Research and continued to receive support from the Navy for 17 years.²¹ Furthermore, he had the backing of other prominent scientists, such as Heidelberger, who not only called upon AAI to speak out but also took matters into his own hands. In response to one USPHS request for him to review a grant application in December 1954, Heidelberger wrote, "Because it has been the policy of the U.S. Public Health Service to judge contracts on the basis of vague charges and political considerations in addition to scientific fitness, I do not propose to waste my time on any consideration of the accompanying application for a Public Health Service grant, at least until authoritative announcement is made that this policy has been abandoned."²²

The AAI Resolutions

The protest resolution authored by the Heidelberger committee in the wake of the April 1954 business meeting was mailed to AAI members in June of that year, following Hobby's statement on USPHS policy. To the surprise of AAI President Alwin M. Pappenheimer, Jr. (AAI '38, president 1954–55) and members of the AAI Council, the resolution "met with considerable disapproval and a number of disturbed letters from members."²³ One member even resigned from AAI in protest of the resolution.²⁴ When the final tally was recorded in August, 133 members had approved the resolution, and 49 opposed it; 252 members did not respond to the mail ballot.²⁵

The opposition to the resolution reflected the anti-communist consensus of the era. The majority of those who disapproved of the resolution expressed concerns that it went too far to protect the rights of communists.

14. *Ibid.*, 28; M. Heidelberger to Chief, Passport Bureau, Department of State, June 11, 1951, Box 3, MH51A6, MH-NLM.

15. Richard M. Fried, *Nightmare in Red: The McCarthy Era in Perspective* (New York: Oxford University Press, 1990), 131; Wang, *American Science in an Age of Anxiety*, 253.

16. Kabat, "Getting Started 50 Years Ago," 27–28.

17. *Ibid.*, 5.

18. *Ibid.*, 5–6, 8–9.

19. *Ibid.*, 13.

20. *Ibid.*, 16.

21. *Ibid.*, 29.

22. M. Heidelberger to F. W. Appel, December 1, 1954, Box 3, MH51A10, MH-NLM.

23. Memorandum from A. M. Pappenheimer and F. S. Cheever to AAI Council Members, July 13, 1954, Box 1, Folder 1, Councillors' Correspondence (Dingle), AAI-UMBC.

24. AAI Council meeting agenda, April 9–10, 1955, Box 1, Folder 2, Councillors' Correspondence (Chase), AAI-UMBC.

25. Memorandum from A. M. Pappenheimer to AAI Members, July 13, 1954, Box 1, Folder 1, Councillors' Correspondence (Dingle), AAI-UMBC.

Although it did not explicitly mention communism, it implied that not even avowed communists should be prohibited from receiving funds, declaring that “even those who are in marked discord with the rest of the people . . . may, through the results of their research[,] render great service, present or future, to the very people with whom they are in discord.”²⁶

Despite the surprising objections from a significant minority of members, Pappenheimer and Secretary-Treasurer F. Sargent Cheever (AAI '50, president 1963–64) were unwilling to let the matter drop. Believing that “the purpose of the resolution and the high moral tone which permeates it are most laudable,” they hoped it might be rewritten so as to receive “unanimous, or practically unanimous, support of the members.”²⁷ The AAI Council agreed and appointed a new committee composed of John H. Dingle (AAI '41, president 1957–58), John F. Enders (AAI '36, president 1952–53), and Frank J. Dixon (AAI '50, president 1971–72) to draft a new resolution.

Committee members recognized the risks involved in issuing a statement of protest. Enders, in a letter written the day before learning that he would be awarded the 1954 Nobel Prize in Physiology or Medicine, pointed out that the Internal Revenue Service (IRS) had recently announced that tax-exempt organizations that “mixed in politics” would lose their tax-exempt status. He did not, however, discourage AAI from taking action. On the contrary, Enders welcomed the opportunity to challenge not only the USPHS policy but also the IRS regulation: “I should be very happy if this action of ours might lead to the legal determination of this [IRS] ruling which appears to me to be particularly dangerous to the free expression of opinion.”²⁸

As the committee attempted to find the appropriate words to protest the USPHS loyalty policy, Pappenheimer wrote Dingle offering his candid thoughts on what most AAI members desired out of the resolution:

I think that many members of our Society feel that present members of the Communist Party or people of proved disloyalty have no business applying for grants from the very government that they are making every effort to overthrow. This of course has nothing

to do with the present resolution but does render the interpretation of Mrs. Hobby's statement somewhat difficult. When, for example, she says “where it is established to the satisfaction of this Department that the individual has engaged or is engaging in subversive activities” what constitutes the satisfaction of her department? Is the mere fact that an individual once played string quartets with a member of the Soviet consulate satisfactory proof of that individual's disloyalty to the United States? Does the fact that an individual was interested ideologically in the Communist Party prior to 1938 indicate that he is disloyal to the United States at the present time and should not receive support for his research work?”²⁹

After two months of deliberating, the committee completed a fifth and final version of the resolution in December 1954. The authors shrewdly omitted any mention of communism or any statement that might be interpreted as defending the rights of



J. Parnell Thomas, “Reds in Our Atom-Bomb Plants,” *Liberty*, June 12, 1947, 15 (See “Protesting the Politicization of Science,” p. 45)

26. Mail ballot attached to the minutes of the AAI Business Meeting, April 13, 1954, AAI-Bethesda.

27. Memorandum from A. M. Pappenheimer and F. S. Cheever to AAI Council Members, July 13, 1954, Box 1, Folder 1, Councillors' Correspondence (Dingle), AAI-UMBC.

28. J. F. Enders to J. H. Dingle, October 20, 1954, Box 1, Folder 1, Councillors' Correspondence (Dingle), AAI-UMBC; “3 U.S. Doctors Win Nobel Award for Work in Growing Polio Virus,” *New York Times*, October 22, 1954, 1.

29. A. M. Pappenheimer to J. H. Dingle, November 3, 1954, Box 1, Folder 1, Councillors' Correspondence (Dingle), AAI-UMBC. Emphasis in original.

communists, allowing AAI to avoid establishing a policy of condemnation or tolerance toward the party. The resulting resolution, a clear and concise statement of principles, was stronger for the omission. It declared that unclassified research grants “should be awarded to investigators on the basis of their competence and integrity and the merits of the problem to be studied.” It also warned of the consequences of violating the principle of scientific freedom: “When research is open and unclassified, the imposition of political or other extraneous requirements on the investigator as a condition for awarding a research grant not only threatens the freedom of science and the principles of the American constitutional government, but may also deprive the nation of achievements of outstanding intellectual ability.”³⁰

The resolution was mailed to AAI members on February 16, 1955, so that they could consider it before the upcoming annual meeting. When it was finally voted on by members at the business meeting in San Francisco on April 12, 1955, the resolution received widespread approval, with only three members dissenting.³¹

The Legacy of McCarthyism in Science

The AAI Council forwarded the resolution to NAS President Detlev W. Bronk, whom President Dwight D. Eisenhower had asked to investigate the growing controversy concerning selection criteria for unclassified research grants. The final NAS report sent by Bronk to the president in 1956 contained recommendations in accord with those outlined in the AAI resolution, namely that applicants for unclassified research grants should be judged solely on “scientific integrity and competence” and “the scientific merits of their program.”³² In August 1956, the Eisenhower administration declared that all executive agencies would adhere to the NAS recommendations for awarding unclassified research grants, effectively ending the NIH policy of withholding funds based on suspicions of disloyalty.³³

We know the names of only a few scientists who were persecuted for their political beliefs, not because there *were* only a few individuals but because we are aware of only those who were prominent enough that they could fight the accusations of communism and have their careers survive intact. Many others, perhaps some of them AAI members, who were denied funding or forbidden international travel because of their political beliefs, likely remained silent to salvage what they could of their reputations. All scientists of the era were affected, at least indirectly, for even those who did not suffer explicit sanctions had to be wary of crossing an unspecified political line. Many, no doubt, adopted self-imposed restrictions on political speech to ensure that their own careers were not threatened. The full extent to which McCarthyism affected AAI members and other scientists can never be measured.

We can be certain, however, that McCarthyism had profound effects on scientists’ professional societies, including AAI, as well as individuals. As navigating public policy became simultaneously more difficult and more necessary for scientists in the 1940s and 1950s, they increasingly relied on professional organizations, such as AAI, FASEB, and the NAS, to take political stands and make policy recommendations, because they could do neither effectively as individuals. One commentator on scientific freedom in the 1950s noted this change and offered the following sound advice: “Let the scientist ... become a functionally operating member of his professional organizations; they need his help, and he may someday need theirs.”³⁴ ■

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

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

30. Resolution attached to memorandum from A. M. Pappenheimer to AAI members, [February 16, 1955], AAI-Bethesda.

31. Minutes of AAI Business Meeting, April 12, 1955, AAI-Bethesda. The minutes do not indicate how many members attended the meeting.

32. National Academy of Sciences, “Report of the Committee on Loyalty in Relation to Government Support of Unclassified Research,” March 13, 1956, AAI-Bethesda. The report is also reprinted as “Loyalty and Research,” *Science* 123, no. 3199 (1956): 660–62.

33. “The White House and Unclassified Research,” *Science* 124, no. 3218 (1956): 398.

34. Carl E. Tausch, “The Unlisted Freedom: Science,” *Scientific Monthly* 75, no. 1 (1952): 12–18, quote from 18.

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.

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



Mary Hewitt Loveless's passport photo, 1955

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



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

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 fraction⁹ and demonstrated that even nonallergic patients produced it when injected with pollen extract.¹⁰

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 Hebal, 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

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



Stinger being extracted from hand

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



Honey bee

Wikimedia Commons; Photo by Daniel Schwen

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

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



Mary Hewitt Loveless as featured in “August’s Deadly Stings,” *Life*, August 9, 1963, p. 57



Mary Hewitt Loveless, 1946
Medical Center Archives of NewYork-Presbyterian/Weill Cornell

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.

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 sacks 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

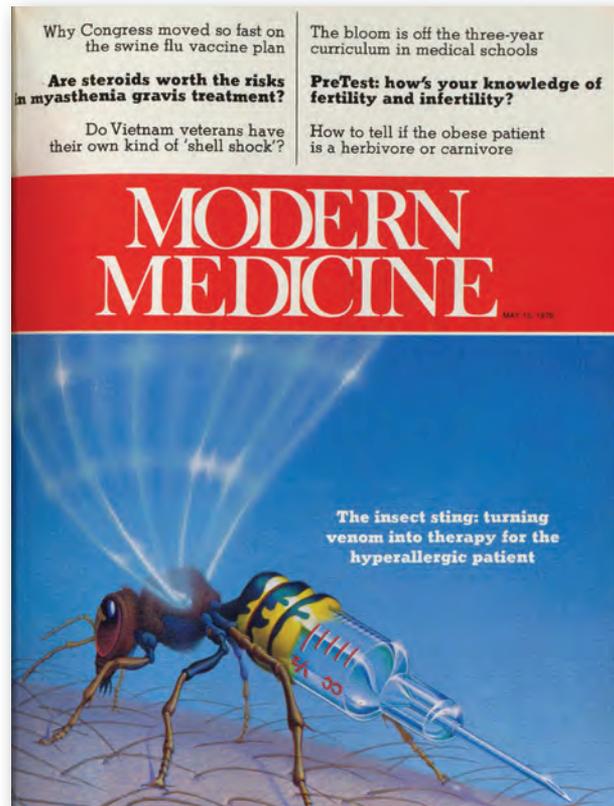
The broader scientific community did not begin to embrace venom therapy until 1974, when, almost 20 years after Loveless first suggested using pure venom, Lawrence M. Lichtenstein (AAI '67), Martin D. Valentine (AAI '72), and Anne Kagey-Sobotka (AAI '78) of the Johns Hopkins University School of Medicine 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,



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

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



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

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

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



Honey bees on honeycomb

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

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

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.

AAI Looks Back

The Founding of AAI Summer Courses in Immunology

By John S. Emrich, Ph.D.

By the early 1960s, the pace of advances in the field of immunology presented great challenges for researchers to keep abreast of the breakthroughs in the field. Few universities or medical schools offered courses in immunology, and even at those institutions offering courses, other faculty generally found them inaccessible, given their own teaching schedules. Moving to address the challenge, the 1964–65 AAI Council resolved “to provide a brief intensive advanced course in Immunology for University Staff to encourage high standards of research and teaching in Immunology.” Two years in the planning, the first course succeeded in setting the standard for short-course immunology education, a standard that remains intact to this day.

The first AAI Summer Course in Immunology commenced on Monday, July 25, 1966, at Lake Forest College, a small liberal arts college 30 miles north of Chicago on the banks of Lake Michigan. Over the next 13 days, 57 attendees listened to lectures by 18 eminent immunologists covering 12 “basic immunology” topics.

The co-directors, Dan H. Campbell (AAI '38, president 1972–73) and Sheldon Dray (AAI '59, secretary-treasurer 1964–70), organized the course into the still-familiar format: selected topics taught by specialists in each field. The faculty for the first course included Frank J. Dixon (AAI '50, president 1971–72), Justine S. Garvey (AAI '56), Elvin A. Kabat (AAI '43, president 1965–66), David W. Talmage (AAI '54, president 1978–79), and Byron H. Waksman (AAI '50, president 1970–71). Most days featured a morning and afternoon session, each dedicated to a particular topic, although organizers scheduled a few

days with only one session to enable students to continue discussions with senior investigators “in an informal workshop type environment.” The following topics were covered at the first course:

Antibodies: nature, structure, synthesis; Antigen-antibody reactions; Antigens; Cellular aspects of immunologic responsiveness and unresponsiveness; Complement; Hypersensitivity; Immunogenetics; Immunological methods; Immunology of infections; Immunopathology and autoimmune phenomena; Transplantation Immunology; and Tumor immunology

Although founded primarily for university instructors and investigators with M.D.s and Ph.D.s who did not have access to immunological training, the AAI Summer Courses in Immunology have evolved over the subsequent 48 years to address the needs of the broader immunology enterprise. Attendees today hail from the United States and abroad and from industry as well as academia. Students new to the discipline or those seeking more information to complement general biology or science training attend the AAI Introductory Course in Immunology. The Advanced Course is directed toward advanced trainees and scientists who wish to expand or update their understanding of the field. Both courses offer intensive six-day instruction by world-renowned immunologists. In 2015, the Introductory Immunology Course will be located in Long Beach, California, and the Advanced Immunology Course will take place in Boston, Massachusetts.

To view the faculty and locations of recent AAI summer courses, visit www.aai.org/Education/Courses/Past_Courses/index.html.

IMMUNOLOGY 2015™ in New Orleans, Louisiana, featured an exhibit chronicling notable developments in Louisiana's medical and public health history. Below is an expanded version of the text accompanying the exhibit.

Immunology at the Mouth of the Mighty Mississippi

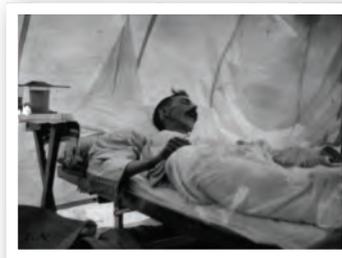
Diseases and Institutions that Shaped Research in Louisiana

by John Emrich

Louisiana has endured centuries of epidemics, outbreaks, and endemic diseases, chiefly in its most populace city, New Orleans. The city is known worldwide for its revelry and rich culture—the pentimento for the various flags that have flown over her since the French first began colonizing the region in the late seventeenth century. In the early nineteenth century, the city became the third largest city in the United States and one of the wealthiest because its bustling port at the mouth of the Mississippi River was the intersection of trade between the nation's interior and the Caribbean, South America, Europe, and beyond. Here, we highlight diseases and institutions that have shaped the medical, public health, and social history of the state.

Diseases

Louisiana, because of its subtropical climate and home, near the mouth of the “Mighty Mississippi,” to the premier southeastern port in the United States, has been the site of many lethal and chronic communicable diseases, including yellow fever, malaria, hookworm, Hansen's disease, and bubonic plague. The presence of these diseases has channeled the current of biomedical research in the state.



Yellow fever patient in hospital
*Images from the History of Medicine,
National Library of Medicine*

deaths between 1817 and 1905.¹ An epidemic in 1878 began in the port of New Orleans and spread up the Mississippi River to the American Midwest, infecting more than 110,000 and killing at least 20,000.² An occurrence in 1905 marked the last yellow fever epidemic in the United States. By this time, the transmission cycle was understood, and public health campaigns, including mosquito prevention and eradication, limited spread of the disease before the first successful vaccine was developed in the 1930s.

Epidemics and Outbreaks

Yellow Fever. An acute infection caused by an RNA virus spread, primarily by the female *Aedes aegypti* mosquito, yellow fever was one of Louisiana's deadliest diseases before the early twentieth century. The mosquitoes carrying the disease typically hitchhiked to Louisiana aboard trading ships from their native Caribbean habitat. Mortality rates climbed as high as 60 percent during some epidemics, and in the New Orleans region, the disease was responsible for more than 41,000



Plague epidemic in New Orleans,
1913–1914
*Images from the History of Medicine,
National Library of Medicine*

Bubonic Plague. In late June 1914, a bubonic plague outbreak in New Orleans was caused by rats from a cargo ship at the New Orleans Stuyvesant Docks.³ In August, at the height of the outbreak, cases were reported at a rate of one every three days. A coordinated response by health officials, led by the U.S. Public Health Service, suppressed the outbreak by year's end through a combination of medical intervention and rat-reduction programs, which included “rat-proofing,” or destroying, hundreds of buildings

1. Infectious Disease Epidemiology Section, Louisiana Office of Public Health, “Yellow Fever,” *Epidemiology Annual Report*, 1934, http://www.dhh.state.la.us/assets/oph/Center-PHCH/Center-CH/infectious-epi/Annuals/LaIDAnnual_YellowFever.pdf (accessed June 22, 2015).

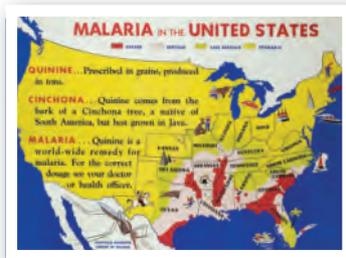
2. “Louisiana Medical Saga: The New Orleans Trilogy,” Public Health Service Hospitals Historical Collection, 1895–1982, Box 8, Folder 7, National Library of Medicine, Bethesda, MD.

3. “Plague in New Orleans,” *Public Health Report* 28, no. 29 (1914): 1809.

and enacting new housing codes. The 1914–1915 outbreak resulted in 31 reported cases, of which 10 were fatal. New Orleans continued to have infections until the city was declared free of the disease in the late 1920s.⁴

Endemic Diseases

Malaria. Although malaria never reached epidemic levels, it was a constant presence in the state, with a peak rate of 57 cases per 100,000 in 1944.⁵ In 1947, the National Malaria Eradication Program began in the United States, focusing on 13 southeastern states. The program successfully eradicated the disease in the United States in 1951 through the reduction of mosquito-breeding sites and the application of insecticides.⁶ An important breakthrough in malaria research was made at Tulane University School of Medicine in 1911, when Charles C. Bass (AAI '16) successfully cultivated plasmodia in vitro, using human blood.⁷ Bass's technique allowed other researchers to better understand and devise new treatments for the disease.



“Malaria in the United States”
Images from the History of Medicine,
National Library of Medicine

Hookworm Infections. Bass was also responsible for calling attention to the impact of hookworm infections in Louisiana, especially in rural children with continuous infection. He recognized growth and developmental problems resulting from the infected children's loss of iron and protein.⁸ Through a series of studies in 1910 at Tulane, Bass,

who was previously a country doctor, determined that the high rate of infection in rural communities was attributable to the geology of central and northern Louisiana, specifically the sandy soil; poor access to privies; and the “habit among children...of going barefoot.”⁹ That same year, a Rockefeller Foundation report found that nearly 40 percent of the population in the South was infected with hookworms, validating Bass's assertions. Within a few years, a public health and education campaign eliminated these occurrences.¹⁰



Head of the hookworm *Necator americanus*
Centers for Disease Control and Prevention/
Dr. Mae Melvin

Hansen's Disease (Leprosy). This disease was well established in Louisiana, particularly in southern Louisiana. By the late 1880s, high incidence rates (4.5/100,000) in the state, especially in South “French” Louisiana, led to the creation of the Louisiana Leper Home in Carville to treat patients and research the disease. Infection rates continued to rise until the late 1920s (12/100,000), with the highest rates still observed in French Louisiana. Antibiotic treatments beginning in the 1940s successfully brought incidence in the state to near zero by the 1970s.¹¹



Hansen's disease research
Images from the History of Medicine,
National Library of Medicine

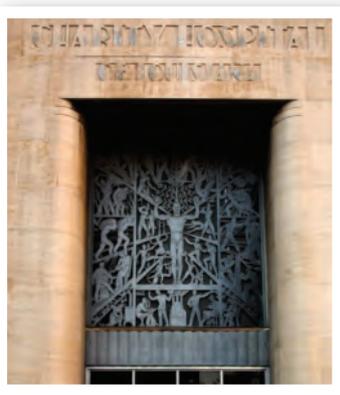
- Infectious Disease Epidemiology Section, Louisiana Office of Public Health, “Plague,” *Epidemiology Annual Report*, 2014, http://www.dhh.state.la.us/assets/oph/Center-PHCH/Center-CH/infectious-epi/Annuals/Plague_LaIDAnnual.pdf (accessed June 22, 2015).
- Infectious Disease Epidemiology Section, Louisiana Office of Public Health, “Malaria,” *Epidemiology Annual Report*, 2013, http://www.dhh.state.la.us/assets/oph/Center-PHCH/Center-CH/infectious-epi/Annuals/Malaria_LaIDAnnual.pdf (accessed June 22, 2015).
- Infectious Disease Epidemiology Section, Louisiana Office of Public Health, “Malaria,”
- For more information about Charles C. Bass, see “Country Doctor, Pioneering Parasitologist, and the Father of Preventative Dentistry: Charles C. Bass, M.D. (1875–1975),” *AAI Newsletter*, June 2015, 20–23; C. C. Bass, “A New Conception of Immunity: Its Application to the Cultivation of Protozoa and Bacteria from the Blood and to Therapeutic Measures,” *Journal of the American Medical Association* 57, no. 19 (1911): 1534–35; C. C. Bass and F. M. Johns, “The Cultivation of Malarial Plasmodia (*Plasmodium vivax* and *Plasmodium falciparum*) In Vitro,” *Journal of Experimental Medicine* 16, no. 4 (1912): 567–79.
- Most people infected with hookworms have no symptoms. Minor symptoms include gastrointestinal problems. In serious cases, there is blood loss, leading to anemia and protein deficiency.
- George Dock and Charles C. Bass, *Hookworm Disease: Etiology, Pathology, Diagnosis, Prognosis, Prophylaxis, and Treatment* (St. Louis, MO: C. V. Mosby Company, 1910).
- “Eradicating Hookworm,” The Rockefeller Foundation, <http://rockefeller100.org/exhibits/show/health/eradicating-hookworm> (accessed on June 9, 2015).
- Infectious Disease Epidemiology Section, Louisiana Office of Public Health, “Leprosy (Hansen's Disease),” *Epidemiology Annual Report*, 2008, http://www.dhh.state.la.us/assets/oph/Center-PHCH/Center-CH/infectious-epi/Annuals/LaIDAnnual_Leprosy.pdf (accessed June 22, 2015).

Institutions

Research institutions and medical schools in Louisiana were founded to address the public's vulnerability to a rare confluence of public health threats. Here, we highlight six of the oldest institutions. All have contributed to the growth of immunology research in the state.

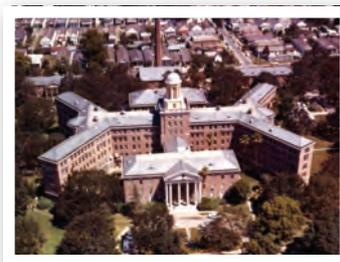
Hospitals and Public Health Institutions

Recognizing the need for a public hospital in New Orleans to serve the poor, a French ship builder residing in the city bequeathed money for what would become the city's venerable **Charity Hospital**. The hospital was founded on May 10, 1739, and operated constantly until 2005, when Hurricane Katrina forced its closure. At that time, Charity Hospital was the second-oldest, continuously operating public hospital in the United States.¹ Charity also served as a teaching hospital for Tulane University and Louisiana State University (LSU) medical schools, where many AAI members held appointments.



Charity Hospital, c. 1939
National Archives and Records Administration

The **United States Marine Hospital** [later named the U.S. Public Health Service (USPHS) Hospital] in New Orleans was founded in 1801, three years after the creation of the U.S. Marine Hospital Service. The initial mission of these entities was to provide medical care to ill and disabled seamen, including those in the U.S. Merchant Marine and U.S. Coast Guard. The mission of the hospital and officers



U.S. Marine Hospital/U.S. Public Health Service Hospital, New Orleans, LA, ca. 1950

Images from the History of Medicine, National Library of Medicine

quickly expanded to assist the city as a leader in clinical research and public health, leading campaigns to control epidemics and outbreaks, especially for yellow fever and bubonic plague. The hospital was closed in 1981, following severe cuts in federal funding.²

The state opened the Louisiana Leper Home in Carville in 1894 and two years later, entered into a contract with the Daughters of Charity of St. Joseph, located in Emmitsburg, Maryland, to care for and treat its patients.³ In 1921, the USPHS took operational control of the institution and established it as the **National Leprosarium**, in accordance with a 1917 federal law mandating the founding of a hospital for leprosy patients.⁴ In addition to treating patients, the facility was updated to become a center for research into Hansen's disease (leprosy) transmission and treatment. Researchers at Carville demonstrated



National Leprosarium, ca. 1950

History of Medicine Division, National Library of Medicine

1. Bellevue Hospital in New York City is the oldest public hospital in the United States. It was founded March 31, 1736.
2. "Louisiana Medical Saga: The New Orleans Trilogy," Public Health Service Hospitals Historical Collection, 1895–1982, Box 8, Folder 7, National Library of Medicine, Bethesda, MD.
3. The Daughters of Charity, a society of apostolic life for women within the Catholic Church, was founded in the seventeenth century with vows of charity, poverty, obedience, and service to the poor. The state was financially responsible for the infrastructure and supplies, and the sisters, who attended to the physical, emotional, and spiritual needs of the community, received a very modest clothing stipend in lieu of a salary. When the sisters arrived at Carville, the resident physician had left—one would not return until National Leprosarium was founded—and because of budget constraints, a weekly doctor visit to Carville had to suffice. The Daughters of Charity officially ended its mission at Carville in 2006. For more information on the role of the Daughters of Charity at Carville, see Daniel Hannefin, "The Daughters of Charity at Carville: 1896–1981," *Vincentian Heritage Journal* 2, no. 1 (1981): 55–80.
4. The original, official name of the institution was United States Marine Hospital Number 66, the National Leprosarium of the United States. In 1917, a federal bill was signed into law "to provide for the care and treatment for those suffering" from Hansen's disease and prevent the spread of the disease. In 1920, the Louisiana Leper Home was selected for the new federal institution.

the efficacy of sulfa drugs (1940s)⁵ and pioneered the use of Rifampin (1970s)⁶ in treating the disease. They also developed the first animal model using armadillos (1971)⁷ for studying the disease. In 1998, the National Hansen's Disease Program was relocated to Baton Rouge, although patients were allowed to choose whether to remain at Carville, receive a lifetime medical stipend, or relocate with the program.



Alton Ochsner, ca. 1953
Images from the History of Medicine, National Library of Medicine

The Ochsner Clinic was opened in New Orleans in 1942, organized by Alton Ochsner and four other professors from Tulane. The clinic was modeled after the Mayo and Lahey Clinics, where specialists from different

disciplines collaborated to diagnose and treat serious medical problems, while also emphasizing physician education. The Ochsner was the first of its kind in the South and enjoyed such rapid success that it was expanded to include a hospital, research facilities, and academic programs. The Ochsner Medical Center remains a cutting-edge clinical and research facility that garners international acclaim.⁸

Medical Schools

Two of the state's oldest medical schools are located in New Orleans. **Tulane University School of Medicine** was founded in 1834 as the Medical College of Louisiana, with the purpose of leading "the advancement of science and the rational treatment of disease." Tulane issued Louisiana's first medical degree in 1835 and was one of two southern institutions identified as "excellently



Tulane University, c. 1900
Library of Congress Prints and Photographs Division

situated in respect to medical education" by the Flexner Report in 1910.⁹ **LSU School of Medicine** was established and opened for classes in 1931. It has expanded over the years and still includes its original building next to Charity Hospital. As the preeminent private and public medical schools in New Orleans, Tulane and LSU have been leaders in clinical and basic research for more than one-half of a century.

Today, Tulane, LSU, and Ochsner are joined by **Tulane National Primate Research Center, LSU Shreveport, Southeastern Louisiana University,** and other smaller research institutions contributing to growth of immunology research in Louisiana. ■



Louisiana State University Medical School, c. 1939
National Archives and Records Administration

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5. G. H. Faget, F. A. Johansen, and H. Ross, "Sulfanilamide in the Treatment of Leprosy," *Public Health Report* 57, no. 50 (1942): 1892–99; G. H. Faget et al., "The Promin Treatment of Leprosy," *Public Health Report* 58, no. 48 (1943): 1729–41; G. H. Faget, R. C. Pogge, and F. A. Johansen, "Promizole in the Treatment of Leprosy," *Public Health Report* 61, no. 26 (1946): 957–60; "Present Status of Diasone," *Public Health Report* 61, no. 26 (1946): 960–63.

6. R. R. Jacobson and R. C. Hastings, "Rifampin-Resistant Leprosy," *Lancet* 2, no. 7998 (1976): 1304–5.

7. W. F. Kirchheimer and E. E. Storrs, "Attempts to Establish the Armadillo (*Dasypus novemcinctus* Linn.) As a Model for the Study of Leprosy. I. Report of Lepromatoid Leprosy in an Experimentally Infected Armadillo," *International Journal of Leprosy and Other Mycobacterial Diseases* 39, no. 3 (1971): 693–702.

8. For more information on the founding and history of Ochsner's, see John Wilds, *Ochsner's: An Informal History of the South's Largest Private Medical Center* (Baton Rouge: Louisiana State University Press, 1985).

9. Abraham Flexner, *Medical Education in the United State and Canada: A Report to the Carnegie Foundation for the Advancement of Teaching, Bulletin Number Four* (New York: Carnegie Foundation, 1910), 148; Vanderbilt University Medical Department (now Vanderbilt University School of Medicine) was the other southern institution identified in the Flexner Report. The Flexner Report brought national attention and scrutiny to the fact that few standards for admission and graduation existed for American medical schools. Shortly after the release of the report, medical schools were forced to raise their standards. Graduates of those schools that failed to conform to the new American Medical Association rating system, motivated by the Flexner Report, were denied medical licenses.

The Emergence of Immunology in Pittsburgh

by Bryan Peery and John Emrich

With IMMUNOLOGY 2014™ taking place in Pittsburgh, Pennsylvania, May 2–6, AAI salutes the current prominence of this city in biomedical research and reflects on the individuals and events contributing to its emergence as an international center for immunology.

Pittsburgh, a major center for immunological research, began its steep ascent to that acclaim just 60 years ago when it attracted a few ambitious, young immunologists to the University of Pittsburgh (Pitt). Among the scientists who arrived in the late 1940s and 1950s were several distinguished members of the American Association of Immunologists (AAI), including Jonas Salk (AAI '47), Frank Dixon (AAI '50, president 1971–72), F. Sargent Cheever (AAI '50, president 1963–64), and Niels Jerne (AAI '65). We chronicle below the achievements of these and other leading immunologists and their roles in shaping the history of immunology in Pittsburgh.

Early Medical Research in Pittsburgh

The discovery of large coal veins in 1833 brought rapid industrialization to Pittsburgh. The transformation of Pittsburgh from a small frontier city to an industrial center was accelerated by the mass production of steel and the heightened demand for that product during the American Civil War.

The city's prominence in higher education and medicine, however, experienced a slower emergence. Western University of Pittsburgh was incorporated in 1813¹ but lacked a sizable enrollment until the turn of the twentieth century. It was not until 1853, following a decade that witnessed endemic typhoid and tuberculosis, as well as multiple outbreaks of smallpox and cholera, that the first chartered public hospital, Western Pennsylvania Hospital, opened its doors.² A group of local physicians chartered the first medical school in 1883, and construction began after 250 shares of stock were sold for \$100 each.³ Western Pennsylvania Medical College opened



Pittsburgh Municipal Hospital, 1939
Pittsburgh City Photographer Collection, University of Pittsburgh

its doors to the first class in 1886. Initially, the college was completely autonomous, but in 1892, it entered into a formal relationship with Western University, officially becoming the Medical Department of Western University, although it was the stockholders, not the university, who had ownership and authority over the department.

Western University underwent dramatic changes in 1908 to raise both the standards and prominence of the school. A new name—the University of Pittsburgh—was adopted, the campus was relocated from its

site in Pittsburgh's North Side section to the Oakland area of the city; and the university formally acquired the medical college. With full control of what was now the University of Pittsburgh School of Medicine, the administration of Pitt hired a new chancellor, Samuel McCormick, who, modeling the institution on the top medical schools in the country, began recruiting accomplished researchers for faculty positions and raising the standards for enrollment and graduation. Facilities and opportunities for clinical research followed, as a new medical school building was opened in 1911, and formal relationships were forged with St. Francis and Mercy hospitals in 1912.

The University of Pittsburgh School of Medicine was not the only medical research institution in the city in these years. The William H. Singer Memorial Research Laboratory was founded at Allegheny General Hospital in 1914 as a research laboratory dedicated to the study of medical and surgical problems. Its staff included Oscar M. Teague (AAI '20), a noted bacteriologist and the first active AAI member in Pittsburgh,⁴ as well as other researchers, who, although not AAI members, published early articles in *The Journal of Immunology (The JI)*.⁵ Western Pennsylvania Hospital also attracted talented immunologists

¹ The Pittsburgh Academy was founded in 1787 as a preparatory school and reincorporated as an institution of higher learning by the Commonwealth of Pennsylvania in 1813.

² Barbara I. Paull, *A Century of Medical Excellence* (Pittsburgh: University of Pittsburgh Medical Alumni Association, 1986), 5–6, 26.

³ *Ibid.*, 11. The price of each share was approximately \$2,400 in today's dollars.

⁴ "Oscar Teague," *The Journal of Immunology* 9, no. 1 (1924): 1–5.

⁵ See, for example, G. R. Lacy and C. C. Hartman, "Specific Reactions of the Body Fluids in Pneumococcal Infections," *The Journal of Immunology* 3, no. 1 (1918): 43–49.

beginning in the 1910s: Jacques J. Bronfenbrenner (AAI '20, president 1942–46) was director of research and diagnostic laboratories at Western Penn from 1913 to 1917, and Arthur P. Locke (AAI '26) and Ralph R. Mellon (AAI '22) were researchers in the laboratories from the 1930s until the 1950s.

The stature of the medical research in Pittsburgh steadily increased from the 1910s through the mid-1940s, but a series of events—the First World War, the Great Depression, and the Second World War—delayed more rapid progress until the end of the 1940s.

Post-War Pittsburgh Renaissance

Turning the University of Pittsburgh School of Medicine into a first-rate research institution had been William S. McEllroy's aspiration since his election as dean by the medical school faculty in 1938.⁶ Born into an affluent Pittsburgh family, McEllroy had personal connections to Pittsburgh's private donors who might turn his dream into a reality.

Resources and focus for McEllroy's plan were soon diverted to the U.S. war effort following the December 7, 1941, attack on Pearl Harbor. With the war's end in 1945, however, McEllroy and Pitt benefitted from the financing and enthusiasm of industrialists and philanthropists united in efforts to usher in "the Pittsburgh Renaissance." Their plan for revitalizing the city included drastically improving public health. McEllroy encouraged the university chancellor to use a portion of the new endowment to fund a university-wide interdisciplinary research program known as the Division of Research in the Natural Sciences.⁷ Furthermore, in 1948, the Graduate School of Public Health was founded at Pitt with a \$13.6 million endowment from the Andrew W. Mellon Education and Charitable Trust.⁸ McEllroy sought to make sure the medical and public health schools' interests were closely aligned. He found an ally in the dean of the new public health program, former U.S. Surgeon General Thomas Parran, Jr.,⁹ who argued that the success of the Graduate School of Public Health would depend on the School of Medicine's receiving the investment necessary to become a top-flight institution.¹⁰

With financial backing and the new Division of Research serving as an indicator of the direction in which Pitt was heading, McEllroy began recruiting researchers from around the country. Convincing established scientists to tie their fates to the nascent program proved difficult because the

appointments lacked status. Younger scientists, however, could be attracted by the promise of independence and a unique opportunity to expedite their advancement through the academic ranks.¹¹ One researcher who was looking for just such an opportunity was Jonas Salk.

Jonas Salk and Polio Research at Pitt

After the war, McEllroy, recognizing virology as a young but promising field that might soon put Pitt on the map, began fundraising for virus research. In 1946, he secured funds from the National Foundation for Infantile Paralysis (NFIP) to start a Virus Research Laboratory.¹² His search for a director of the new laboratory led him to an assistant professor of epidemiology at the University of Michigan School of Public Health, Jonas E. Salk.

Although Salk's credentials were respectable, he was hardly a luminary in 1947, and there was little to indicate that he would become the legend that he is today.¹³ The eldest son of working-class Russian immigrants, Salk grew up in the Bronx, New York, and attended City College of New York during the Great Depression before earning his M.D. from the New York University (NYU) College of Medicine in 1939. At NYU, he studied under William H. Park (AAI '16, president 1918–19) and Thomas Francis, Jr. (AAI '30, president 1949–50), who



Jonas Salk and Julius S. Youngner, ca. 1954

University of Pittsburgh News Services

⁶ Paull, *A Century of Medical Excellence*, 141.

⁷ *Ibid.*, 176.

⁸ *Ibid.*, 165–67; "About," Graduate School of Public Health, University of Pittsburgh, <http://www.publichealth.pitt.edu/home/about>.

⁹ Parran was the sixth surgeon general of the United States, serving under Presidents Franklin Roosevelt and Harry Truman from 1936 to 1948.

¹⁰ Paull, *A Century of Medical Excellence*, 167.

¹¹ *Ibid.*, 176.

¹² *Ibid.*, 178; David M. Oshinsky, *Polio: An American Story* (New York: Oxford University Press, 2005), 109.

¹³ Daniel S. Greenberg, "The Vanishing Heroes of Science," *New York Times*, July 4, 1995, 31.

was then experimenting with using ultraviolet light to produce killed-virus vaccines.¹⁴ After completing a two-year medical internship at Mount Sinai Hospital in New York, Salk contacted Francis in 1942 about a job. The previous year, Francis had become chair of the Department of Epidemiology at the University of Michigan School of Public Health and director of the Influenza Commission of the Armed Forces Epidemiological Board. Francis brought Salk to Michigan, helping Salk secure both a National Research Council Fellowship and a draft deferment.¹⁵

After five years under Francis, Salk grew restless, desiring a promotion and more independence. He and Francis had a cordial relationship, but Francis could offer only an assistant professorship. When McEllroy promised to make Salk an associate professor and head of the Virus Research Laboratory at Pitt in 1947, he immediately accepted the offer.¹⁶

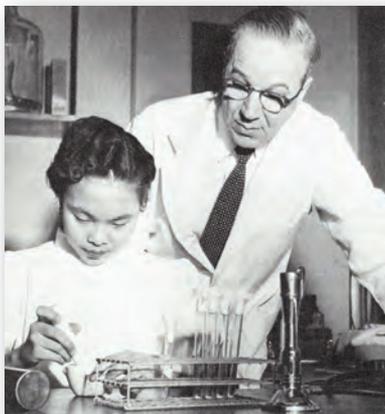
At the time of Salk's arrival in Pittsburgh, the medical school's transition to major research institution was far from complete. Salk soon realized that it fell upon him to be an impetus for change. He later recalled the shock of learning that most of his colleagues "were part-time instructors who earned their living in private practice and had neither the time nor inclination for basic research."¹⁷ He would have to build his laboratory from the ground up—literally. Starting with two rooms and a technician in the basement of Municipal Hospital, he waged what one colleague recalled as "a kind of guerilla war" for space and funding.¹⁸

He continued his investigations into influenza virus but increasingly turned to poliomyelitis virus, at least in part because he knew this research would attract funding.¹⁹ When NFIP approached him in late 1947 about doing the tedious technical work of typing poliovirus, Salk readily agreed to do what senior researchers had shunned. In return, he received large research grants, beginning in 1948, to help him build his laboratory.²⁰ By 1949, his laboratory and

offices had expanded to two floors in Municipal Hospital, he had been promoted to full professor, and he was hiring his own research faculty. One of the scientists whom he brought into his laboratory was Julius S. Youngner (AAI '50) from the University of Michigan, who, as a senior assistant research scientist at the National Cancer Institute, had specialized in cell culture techniques. Youngner would remain an active member of the Pitt faculty for the next 50 years.



Jonas Salk inoculating a young girl
*History of Medicine Division,
National Library of Medicine*



William M. Hammon, ca. 1955
© University of Pittsburgh

By 1951, Salk's laboratory had completed its typing project, concluding that there were three distinct types of poliovirus. The lab shifted its efforts to producing a vaccine. Based on the success that his mentor Francis had had with a killed-virus flu vaccine, Salk chose to pursue a killed-poliovirus vaccine over the attenuated-virus vaccine that the majority of other scientists, including his rivals Albert B. Sabin (AAI '46) and Hilary Koprowski (AAI '46), preferred.

Even within the small community of researchers at Pitt, Salk had competition. In 1950, Parran recruited William McDowall Hammon (AAI '46) to chair the Department of Epidemiology and Microbiology at the Graduate School of Public Health. Unlike Salk, who had no experience with polio research when he was hired to head the Virus Research Laboratory, Hammon had already established himself in the field when Parran convinced him to leave his position as dean of the School of Public Health at the University of California, Berkeley, for Pittsburgh. Wary of both killed-virus and attenuated-virus vaccines, Hammon preferred passive immunization through gamma-globulin injections containing polio-resistant antibodies. He conceded that passive immunization would not prevent infection, but he argued that it could prevent the worst symptom of infection—paralysis. NFIP-funded, double-blind trials involving more than 50,000 children in 1951 and 1952 yielded compelling evidence that passive immunization was a major step in the war against

¹⁴ Oshinsky, *Polio*, 98.

¹⁵ *Ibid.*, 100–101.

¹⁶ *Ibid.*, 107.

¹⁷ Salk quoted in *ibid.*, 109.

¹⁸ *Ibid.*, 110.

¹⁹ *Ibid.*, 110–11.

²⁰ *Ibid.*, 116.

polio. Unfortunately, as Hammon himself pointed out, the immunity produced was only temporary, and the gamma-globulin was in short supply.²¹

Meanwhile, Hammon's passive immunization approach was eclipsed by Salk's March 1953 announcement of the successful completion of the first human trials of his group's killed-virus vaccine.²² The national field trial, which involved more than 1.8 million children and was overseen by Thomas Francis, commenced in June 1954, and, on April 12, 1955, Francis pronounced the vaccine safe and effective.²³ Salk instantly became a celebrity scientist, receiving a Presidential Citation and the Congressional Gold Medal in 1955 and the Albert Lasker Clinical Medical Research Award the following year. Although Salk left Pitt to head the Salk Institute in 1963, his accomplishments of the 1950s cemented Pitt's reputation as a major research center for medical sciences.

Frank Dixon and the "Pittsburgh Five"

In addition to attracting national attention through his own laboratory studies, Salk's administrative work helped contribute to the effort to transform Pitt into a major research institution. As the head of the search committee for a chair of the Department of Pathology in the medical school in 1951, Salk selected a scientist who shared several key characteristics with him: Frank J. Dixon was young, ambitious, and not yet well-known.²⁴

Dixon had grown up in St. Paul, Minnesota, and had attended the University of Minnesota, where he earned his M.D. in 1942 before entering the medical corps of the U.S. Marine Corps and serving in the Pacific Theater. Upon his return to the United States in 1946, Dixon became a research assistant in the Department of Pathology at Harvard. He moved to St. Louis, Missouri, in 1948, where he was an instructor in the Department of



The "Pittsburgh Five," from left to right, Charles G. Cochrane, Joseph D. Feldman, Frank J. Dixon, Jacinto J. Vazquez, and William O. Weigle
The Scripps Research Institute

Pathology at Washington University for two years before being promoted to assistant professor in 1950. The following year, Salk and his search committee offered a full professorship and the chair of the Department of Pathology to Dixon, who, at age 31, became the youngest department head at Pitt.²⁵

As a research assistant at Harvard in 1946, Dixon had developed a new technique for labeling and tracking the location of proteins in the body using radioactive iodine.²⁶ At Pitt, he used this procedure to study serum sickness and soon discovered that the host's antibody immune response to foreign proteins in the injected serum caused deposition of immune complexes in tissues that led to tissue destruction.²⁷ From these results, Dixon made a novel and important conclusion—the body's immune response could have deleterious effects on the health of the host. Dixon's careful methodology in the study of serum sickness and kidney disease served as a paradigm for immune complex-mediated disease pathogenesis and established the field of immunopathology, a discipline critical to the understanding of autoimmune diseases, such as lupus erythematosus and rheumatoid arthritis.

In his second year at Pitt, Dixon received the Theobald Smith Award of the American Association for the Advancement of Science, an honor bestowed upon the most outstanding medical researcher under the age of 35. As chair of the pathology department, he sought to change the culture of the department



Frank J. Dixon
The American Association of Immunologists Records, Center for Biological Sciences Archives, University of Maryland, Baltimore County

²¹ Charles R. Rinaldo, Jr., "Passive Immunization against Poliomyelitis: The Hammon Gamma Globulin Field Trials, 1951–1953," *American Journal of Public Health* 95, no. 5 (2005): 790–99.

²² Jonas E. Salk, "Studies in Human Subjects on Active Immunization against Poliomyelitis. I. A Preliminary Report of Experiments in Progress," *Journal of the American Medical Association* 151, no. 13 (1953): 1081–98.

²³ "Text of the Statements on Dr. Salk's Vaccine Evaluation," *New York Times*, April 13, 1955, 22.

²⁴ Paull, *A Century of Medical Excellence*, 180; Leah Kauffman, "California Dreaming: Frank Dixon Dreams Immunopathology and White Sand Beaches," *Pitt Med*, January 2002, 27, http://pittmed.health.pitt.edu/jan_2002/ca_dreaming.pdf.

²⁵ Michael B. A. Oldstone, "Frank James Dixon, 1920–2008," *Biographical Memoirs* (Washington, DC: National Academy of Sciences, 2009), 4–5.

²⁶ Shields Warren and Frank J. Dixon, "Antigen Tracer Studies and Histologic Observations in Anaphylactic Shock in the Guinea Pig," *American Journal of the Medical Sciences* 216, no. 2 (1948): 136–45.

²⁷ Frank J. Dixon, Jacinto J. Vazquez, William O. Weigle, and Charles G. Cochrane, "Pathogenesis of Serum Sickness," *A.M.A. Archives of Pathology* 65, no. 1 (1958): 18–28; William O. Weigle and Frank J. Dixon, "Relationship of Circulating Antigen-Antibody Complexes, Antigen Elimination, and Complement Fixation in Serum Sickness," *Proceedings of the Society for Experimental Biology and Medicine* 99, no. 1 (1958): 226–31.

so that it reflected both his youth and his interest in research. He brought in young scientists as fellows and assistant professors and allowed them to devote themselves to laboratory research by hiring part-time faculty to take care of many of the teaching and clinical responsibilities.²⁸ Dixon believed that enthusiasm for research was contagious, explaining, “Nothing is more valuable than for a student to sit down and talk to a young researcher, six or seven years his senior, and feel the excitement that comes from scientific inquiry.”²⁹ One instance in which Dixon’s teaching philosophy bore fruit was in the case of William O. Weigle (AAI ’57), a laboratory technician from a working-class family, whom Dixon encouraged to pursue a Ph.D. at Pitt.³⁰

In 1960, Dixon received an offer from Edmund Keeney, director of the then relatively unknown Scripps Clinic in La Jolla, California, to establish a Division of Experimental Pathology. As long as Dixon could secure outside funding, he and his researchers would be free of administrative and teaching responsibilities and devote themselves to full-time research. Dixon, Weigle, Charles G. Cochrane (AAI ’61), Joseph D. Feldman (AAI ’63), and Jacinto “Joe” Vazquez (AAI ’59)—known as the “Pittsburgh Five”—left Pitt for the Scripps Clinic in 1961, taking with them six post-docs and several members of the support staff.³¹ Together, they laid the foundation for the world-renowned Scripps Research Institute. Dixon’s pioneering achievements in immunopathology were formally recognized when he was awarded the Gairdner Foundation International Award in 1969 and the Albert Lasker Basic Medical Research Award in 1975.

F. Sargent Cheever

When William McEllroy retired in 1958, he was succeeded as dean of the School of Medicine by Francis Sargent Cheever. A fourth-generation Boston physician, Cheever attended the prestigious Groton School and received both his B.A. and M.D. from Harvard University.³² Following a two-year medical internship at Presbyterian Hospital in New York, he returned to Harvard in 1939 as a research fellow in

bacteriology, rising to the rank of assistant professor by 1946. In 1950, acceding to an invitation from his Harvard classmate William Hammon to join him at Pitt, Cheever became a professor of epidemiology and microbiology in the Graduate School of Public Health.³³

Shortly after arriving at Pitt, Cheever sought a second appointment in the Department of Bacteriology in the School of Medicine. Eager to add another first-rate researcher to the medical school faculty and to further the relationship between the medical and public health schools, McEllroy made Cheever a lecturer in the Department of Bacteriology in 1951. Cheever was well-liked by his colleagues in both schools, and his patrician background allowed him to run in the same social circles as wealthy Pittsburgh donors who soon looked to Cheever as a spokesman for the university. These qualities led Parran to encourage Cheever to prepare for a role in administration, so when McEllroy announced in January 1958 that he would retire at the end of the term, Cheever was a natural choice as his successor.³⁴



F. Sargent Cheever, ca. 1962
FASEB Archives



Niels K. Jerne
FASEB Archives

Cheever excelled in the position and oversaw the expansion of the medical school during his 11-year tenure. The highlight of these years was the formal integration of the medical and public health schools with several Pittsburgh hospitals into the University Health Center [now the University of Pittsburgh Medical Center (UPMC)]. From 1970 to 1974, Cheever served as president of the new medical center.

Niels Jerne

As dean of the School of Medicine, Cheever succeeded in attracting stellar faculty to Pitt, including Niels K. Jerne, who became chair of the Department of Microbiology in the School of Medicine in 1962. Jerne had already established himself as a preeminent immunologist at the time of his arrival. He had been a researcher at the State Serum Institute in Copenhagen for 10 years before joining Max Delbrück’s laboratory at the California Institute of Technology in 1954, where he published

²⁸ Paull, *A Century of Medical Excellence*, 180; Oldstone, “Frank James Dixon, 1920–2008,” 5.

²⁹ Dixon quoted in Paull, *A Century of Medical Excellence*, 181.

³⁰ Oldstone, “Frank James Dixon, 1920–2008,” 5.

³¹ Kauffman, “California Dreaming,” 29; Jenelle Pifer, “We Knew You When: Charles Cochrane and the Pittsburgh Five,” *Pitt Med*, Fall 2012, 39, http://pittmed.health.pitt.edu/Fall_2012/alumni.pdf.

³² “Pitt Names New Dean of Medicine,” Press Release, January 30, 1958, *Documenting Pitt*, University of Pittsburgh, http://digital.library.pitt.edu/cgi-bin/t/text/text-idx?c=pitt_pressreleases;view=to;idno=pittpressreleases19580018.

³³ Paull, *A Century of Medical Excellence*, 208; “Cheever, Francis Sargent,” *American Men and Women of Science*, 14th ed. (1979), 2:801.

³⁴ Paull, *A Century of Medical Excellence*, 208–10.

the landmark paper, “The Natural-Selection Theory of Antibody Formation”³⁵ in 1955. Jerne next headed the Biological Standards and Immunology sections of the World Health Organization in Geneva from 1956 to 1962, but, wishing to return to academic life and his immunological research, he seized the opportunity to chair the Department of Microbiology at Pitt when it arose in 1962.

The change of venues paid immediate dividends. Jerne, regarded as one of immunology’s greatest theorists, returned to the laboratory and made an important technical innovation. With Albert A. Nordin (AAI ’72), a post-doc at Pitt, he developed the plaque-forming cell assay—often called the Jerne plaque assay—which advanced the study of immunology at the cellular level by allowing researchers to see and enumerate antibody-producing cells in an agar plate.³⁶

Jerne left Pittsburgh in 1966, succeeded at Pitt by Julius Youngner, who chaired the Department of Microbiology from 1966 to 1989. Jerne returned to Europe and directed the Paul Ehrlich Institute before becoming the founding director of the Basel Institute for Immunology in 1969. In recognition of his major contributions to the field of immunology, he was awarded the 1984 Nobel Prize in Physiology or Medicine.

New Directions: 1980s–Present

Neither the growth of the medical sciences at Pitt nor the role of AAI members in advancing it ended in the 1960s. Donald N. Medearis (AAI ’65) succeeded Cheever as dean of the medical school, serving from 1969 to 1974. One of his most significant acts as dean was recruiting Thomas Detre to head the Department of Psychiatry in 1974.³⁷

As senior vice chancellor of the health sciences from 1984 to 1998, Detre left a lasting legacy on UPMC. He oversaw the transformation of UPMC into a research hub of international renown by establishing several research institutes, including the Pittsburgh Transplantation Institute (renamed the Thomas E. Starzl Transplantation Institute in 1996) and the University of Pittsburgh Cancer Institute (UPCI) in 1985.³⁸

Under the direction of Ronald B. Herberman (AAI ’69), UPCI was designated a Comprehensive Cancer Center by the National Cancer Institute, five years after its establishment, making it the youngest center to receive such a distinction.³⁹ Moreover, it was at UPCI that immunology began to emerge as one of the more significant areas of basic research at Pitt in the late 1980s. By

1997, the interdepartmental Graduate Program in Immunology had received accreditation and was authorized to award Ph.D. degrees.⁴⁰ In January 2002, the School of Medicine established the Department of Immunology and appointed Olivera J. Finn (AAI ’83, president 2007–2008) its founding chair.⁴¹

Although there is now a permanent home for the study of immunology at Pitt, studies in the field and AAI members remain ensconced in several departments and institutes across the university. Since 1997, Charles R. Rinaldo, Jr. (AAI ’78), has served as chair of the Department of Infectious Diseases and Microbiology in the Graduate School of Public Health, the position once held by William Hammon. Recognizing parallels between the mid-century work on polio carried out by his predecessors at Pitt and his own research on HIV and AIDS, Rinaldo declared in a 2004 interview, “I look to history to help me look to the future.”⁴²

Salk, Dixon, Cheever, Jerne, and the many other AAI members who have called Pittsburgh home helped to establish the city as a major center for immunological research. In turn, Pittsburgh has contributed much to AAI. Five past presidents and one current councillor, Joanne L. Flynn (AAI ’96, councillor 2013–present), have spent at least some of their professional years in Pittsburgh. Beginning with Arthur Locke, who became an associate editor of *The JI* in 1936, Pittsburgh immunologists have worked to ensure that *The JI* remains the preeminent journal in the field, most notably Joseph Feldman, who served as editor-in-chief from 1971 to 1987. Together, these immunologists have left behind an enduring legacy that continues to inform the work of immunologists the world over. ■

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Olivera J. Finn, 2009
AAI Archives

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⁴⁰ Olivera J. Finn and Russell D. Salter, “Immunology in Pittsburgh,” *Immunologic Research* 36, nos. 1–3 (2006): 2.

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FEATURE

History of Immunology in the Nation's Capital

IMMUNOLOGY 2017™ featured the American Association of Immunologists (AAI) Timeline along with a special exhibit chronicling major trends and milestones in the emergence of the Washington, DC, region as a major center of immunology research over the last century. The exhibit featured many of the institutions, members, and external forces that have helped shape the field in the nation's capital.



Institutions



*USPHS Hygienic Laboratory, ca. 1920s
National Library of Medicine*



*Aerial view of the Clinical Center, NIH, 2014
NIH*

At the beginning of the 20th century, immunology research institutions in the Washington, DC, area were overwhelmingly government laboratories, including the Walter Reed General Hospital, U.S. Army Medical School [now Walter Reed Army Institute of Research (WRAIR)], and the U.S. Public Health Service Hygienic Laboratory—now the National Institutes of Health (NIH).

Today the region is home to world-renowned public and private research institutions, an expanding biotechnology corridor, and a growing number of scientific societies, foundations, and other non-profits. The IMMUNOLOGY 2017™ exhibit explored the region's immunology-related institutions through a brief history of the NIH, mapping of AAI member institutions, and a spotlight on the area's biotech industry and diverse non-profit community.

AAI Annual Meetings

Washington, DC, has been home to the AAI annual meeting 10 times. The city was host to the second annual meeting, which took place on May 10, 1915, at the Willard Hotel, and featured a program of 19 original scientific papers. The recently completed IMMUNOLOGY 2017™ meeting stretched over five days at the Washington Convention Center and included over 125 scientific sessions and three days of poster presentations.

AAI Members

AAI welcomed its first Washington, DC, members in 1916, and witnessed membership growth throughout the metropolitan area over the next eight decades. The region has been a stronghold of AAI membership representing all career stages, from early-career trainees to established investigators and emeritus members.

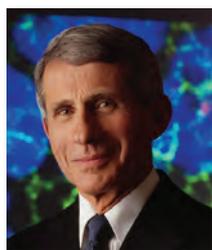
The strength and diversity of clinical and basic research in the area led some AAI members to make the region home for their entire careers. Of those, four have been AAI members for 50 or more years: Samuel B. Formal (Walter Reed Army Medical Center and WRAIR), Joseph A. Bellanti (Georgetown University Medical Center), Rose G. Mage (NIH), and Abner Louis Notkins (NIH).

AAI members in the region have received some of the highest honors in the field. They include a Nobel Laureate—Baruj Benacerraf (NIAID)—and eight Lasker Award recipients—Anthony S. Fauci (NIAID), Jules Freund (NIAID), Maurice R. Hilleman (WRAIR), Michael Potter (NCI), John B. Robbins (NICHD, FDA, and NIH), Albert B. Sabin (FIC†), Rachel Schneerson (NICHD, FDA, and NIH), and Joseph E. Smadel (WRAIR and NIH).

NIH Leadership

The history of AAI members serving as NIH institute and center directors dates from the late nineteenth-century. The eleven past directors have included three at the Hygienic Laboratory, the first director of the NIH, multiple directors of NIAID and NCI, and Ruth L. Kirschstein, who was the director of NIGMS and later the acting director of both the NIH and NCCIH.

Today, three current NIH directors are AAI members: Anthony S. Fauci (NIAID), Richard Hodes (NIA), and Stephen I. Katz (NIAMS).



Anthony S. Fauci
NIAID, NIH



Richard J. Hodes
NIA, NIH



Stephen I. Katz
NIAMS, NIH

External Forces

As the center of the nation's government, Washington, DC, is also the hub of federal scientific funding and of social and political advocacy for research.

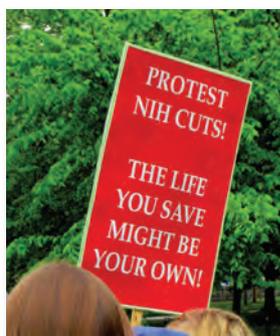
The most important piece of biomedical funding is the NIH budget, which received its first line item in the federal budget in 1938—\$464,000. The dramatic increase in the NIH budget following World War II marked a time of rapid expansion in the number of institutions carrying out basic and clinical immunology research as well as in the growth in AAI membership in the area. Although the NIH budget continued to increase throughout the twentieth century, including the doubling (1998–2003), the past decade has seen a degree of uncertainty in the funding landscape never before experienced by researchers.



30,000 letters at the White House containing 10¢ contributions to combat polio, 1938
Library of Congress

The city has been a focal point for many social movements. From Congressional hearings, to mailing of dimes to the White House for polio research to AIDS activism and creation of the iconic AIDS quilt to more recent rallies and protests supporting scientific funding and research, advocacy for research and patients has been a small but important movement that has taken place in the region.

For over 100 years, the greater Washington, DC, area has been a primary contributor to AAI and the immunology community. Today, it is home to an increasingly diverse array of public and private immunology-related research institutions and non-profits, thousands of researchers, and leaders in the scientific community—not to mention the headquarters of AAI and many other scientific societies. As the focal point of federal biomedical research, funding, policy, and activism, the nation's capital in 2017 offered AAI meeting attendees a vivid reminder of its unique and enduring relevance to our field and to the future of scientific advancement.



March for Science, 2017
AAI

† FIC—Fogarty International Center, NIH



FEATURE

A BRIEF HISTORY OF BOVINE IMMUNOLOGY IN TEXAS

THE OLD CHISHOLM WITH SUBSIDIARY TRAILS IN TEXAS

Away from the large metropolitan areas of Texas, grazing herds of cattle have been such a fixture that their visage has been an emblem of the 28th state for the past century. Since the mid-19th century, cattle ranching has been more than a way of life; it is an economic engine, producing beef, milk, and leather. As the cattle industry has made up a significant segment of the state's economy for a century and a half, Texas has also been a leader in bovine immunological research. With IMMUNOLOGY 2018™ in Austin, Texas, we take a look at this research through four important historical advances, beginning with "Texas fever," a disease specific to the state that almost permanently ruined the industry, and concluding with a modern breakthrough in AIDS research using bovine models.

Texas cattle industry

In the 16th century, early Spanish explorers first brought cattle to the area that is now Texas. Some of the livestock that were meant to sustain both the expeditions and permanent missions escaped and formed the basis for enormous wild herds that became Texas Longhorns. Until 1780, the market for beef from Texas was very limited because of Spanish restrictions on trade with French colonies. The United States annexed Texas in 1845, but it was not until the end of the Civil War that the age of the great cattle drives began with the Chisholm Trail, leading to the markets in Kansas. That legendary era only lasted approximately 20 years until the proliferation of barbed wire and the expansion of the railroad made the drives difficult and unnecessary. Today, Texas still leads the nation in cattle production, with over 12 million head at the beginning of 2018.²

Because cattle ranching has always been vulnerable to disease, the understanding of how to prevent and cure infections has saved the industry on multiple

occasions. Veterinary researchers and immunologists have been instrumental in investigating the causes of cattle diseases and developing methods to combat them.

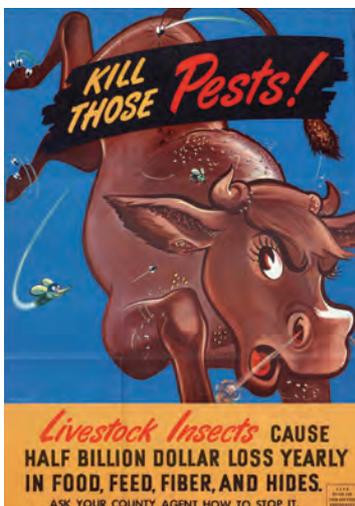
Theobald Smith and Texas fever (bovine babesiosis)

Before the Civil War, southern cattle were often considered "scrawny" or lean compared with those in the north.³ Once the cattle drives from Texas to the north began, the reason for this became clear, as northern cows started to fall ill after

mingling with southern herds. Symptoms for affected cows included increased basal temperature, pulse, and respiration; loss of appetite; and in some cases, hemoglobinuria for a duration of eight to 10 days.⁴ Mortality rates for northern cattle were as high as 90%, giving rise to legitimate fear of what soon became known as Texas fever.⁵

States quickly outlawed Texas cattle drives across their borders and instituted quarantines against the Texas herds, jeopardizing the entire industry if a solution could not be found.

Through years of observation, ranchers had long believed that ticks played an important role in the transmission of Texas fever.



*Livestock pest control poster, c. 1948
U.S. Department of Agriculture*

Their homegrown theory, however, was dismissed for decades by researchers at the U.S. Department of Agriculture (USDA) as lacking “the slightest foundation.”⁶ The first researcher to give the tick theory serious credence was Theobald Smith (AAI '20), working on behalf of the USDA Bureau of Animal Industry. In 1899, Smith developed a simple experiment to test the tick vector theory of Texas fever transmission.

First, he set up pens with healthy northern cattle, introduced tick-laden southern cows, and observed the northern cattle for signs of illness. Within four months, three quarters of the northern cattle had died of Texas fever.

Smith then painstakingly removed all of the ticks from the southern cows and moved them to a tick-free pen with fresh northern cattle, and again observed the northerners for signs of illness. This time they were all asymptomatic.⁷

The ranchers' theory was vindicated, and Smith had proven, for the first time, that ticks could act as a disease vector. Smith published his findings in 1893, and the same year, the Texas state legislature established the Livestock Sanitary Commission [renamed the Texas Animal Health Commission (TAHC) in 1959] to fight Texas fever.⁸

Smith continued his work on Texas fever and, in experiments over the next four years, he isolated and identified the pathogen that the ticks were carrying. He named this protozoan *Pyrosoma bigeminum*, but the genus is now known as *Babesia*, and either *Babesia bovis* or *Babesia bigemina* can cause the disease.⁹ In addition, he identified mechanisms of immunity to the disease among northern and southern cattle populations.¹⁰ This research suggested that vaccines could be possible, but Smith also developed a practice that was immediately

effective: dipping cattle in chemical baths containing an arsenical solution to kill any attached ticks. A cow with no ticks cannot transmit Texas fever to other cows. Because cattle fever ticks are host specific, simply removing cattle from an area will cause the ticks there to starve. This strategy, combined



Theobald Smith
Library of Congress

with federally mandated dipping, reduced the tick population enough that most cattle quarantines could be lifted by 1916.¹¹ Although cattle fever ticks were considered eradicated in the United States by the 1960s, acaricide-resistant ticks from Mexico are currently re-emerging in South Texas.

Brucellosis

Once Texas fever was under control, another persistent problem began to vex the cattle industry: bovine brucellosis—a highly contagious disease that can decimate a herd through spontaneous abortions and decreased milk production; cause weight loss, loss of

young, and infertility; and spread lameness throughout American cattle herds. By the mid-1930s, it was estimated that the majority of herds had infection rates of 13–16%.¹² In addition, humans can also contract brucellosis from infected cattle.

Called “undulant fever” in humans for the waves of temperature variation, cases of brucellosis in the United States went from only 46 in 1926 to 1,787 in 1934.¹³ People most often caught brucellosis by drinking raw milk, a problem that Karl F Meyer (AAI '22, president 1940–41) largely solved by 1931 by promoting diagnostic tests and pasteurization. In Texas, however, livestock workers were the primary victims through their close contact with infected cattle.¹⁴ Bovine brucellosis proved difficult to combat effectively: in the 1930s and 1940s, arsenical and mercurial drugs were tried, as well as therapeutic vaccines, but they produced very limited success.¹⁵ Dozens of articles on aspects of *Brucella* appeared in *The Journal of Immunology* at this time. Although Texas began a calf-vaccination program in 1959, compliance rates remained low as the vaccine sensitized the calves to the standard serum agglutination test.¹⁶ In 1980, the TAHC instituted new standards developed by the USDA, and just 10 years ago, Texas was finally declared free of bovine brucellosis.¹⁷

Anthrax

The soil of the southwestern Texas plains is not fertile ground for many crops, but it does produce one unwanted harvest: anthrax spores. In the 1950s and '60s, bone-meal production, a process in which bones of cattle that had died from anthrax were ground and spread in the low-acid soil of pastures as a feed component, unwittingly seeded the soil with the spores, creating a new and extended problem for the cattle industry.¹⁸



Dipping steers to remove ticks
Cattle Raisers Museum

Unlike the bacteria that cause Texas fever and brucellosis, *Bacillus anthracis* is a remarkably tenacious organism, able to survive for decades in spore form. Typically, the spores are buried at a safe depth, but a wet spring—followed by



Bacillus anthracis
Centers for Disease Control and
Prevention

a dry summer—sets the stage for their emergence after the drought breaks.¹⁹ As there is no way to eradicate *B. anthracis* from the environment, the disease must be managed through vaccination or culling.

Robert Koch identified the bacterium in 1876, and Louis Pasteur

subsequently developed an anthrax vaccine in 1881. In 1935, Max Sterne isolated an avirulent strain of *B. anthracis* and produced an effective, attenuated vaccine with it that is still in use today. Most cattle, however, will not be exposed to anthrax spores, so the culling of infected animals has been a more economical option. One of the first AAI members in Texas, Kenneth L. Burdon (AAI '36), founding

chair of microbiology at Baylor College of Medicine, spent much of his career researching spore-producing bacteria and developed methods of differentiating *B. anthracis* from other species in the genus. Accurate diagnosis in both human and cow from only clinical signs is very difficult, so Burdon's criteria have been important in effectively identifying infection.

Human immunology and HIV

Texas cattle have recently proven to be allies in human immunology research, including the fight against HIV. In 2013, as part of a widespread team of researchers, Waitthaka Mwangi (AAI '02) and Michael Criscitiello (AAI '01) at the Texas A&M University College of Veterinary Medicine & Biomedical Sciences, found that bovine antibodies possess unique structures of exceptionally long complementarity-determining regions (CDRs) that form “stalk” and “knob” domains.²⁰ The knob on the long CDR H3 turned out to be almost completely responsible for binding to viruses, leading researchers to wonder whether any of the structures they target exist on human pathogens.²¹

They did not have to wonder long. A new study, also involving Mwangi and Criscitiello, has now elicited broadly



Cow used by Mwangi in bNAb research
Waithaka Mwangi, Texas A&M University
College of Veterinary Medicine
& Biomedical Sciences

antigenically mimics the HIV envelope glycoprotein, rapidly eliciting broad and potent serum antibody responses.²² Ten to twenty percent of people with HIV also produce bNAbs, but typically only after two years of infection and not at a rate sufficient to produce therapeutics.²³ The cow study showed 96% neutralization breadth in only 381 days.

Cows may have evolved the ability to produce bNAbs so quickly as a result of their complex digestive tracts: the resident bacteria necessary to break down tough grasses

neutralizing antibodies (bNAbs) in cows. These antibodies, which are capable of neutralizing multiple HIV strains, can be produced in cows much faster than is currently possible in human experimentation. The cows at A&M received immunizations with a protein that

pose an infection risk if they escape the gut, so a versatile mechanism to produce antibodies would be beneficial to them. The antibodies that the cows produce have promise to work in humans—“with a few tweaks,” according to Criscitiello.²⁴ This study may also have potential as a model for production of antibodies for other human diseases.

Although the cattle industry in Texas today is almost unrecognizable from its 19th-century roots, many of the challenges of keeping cows healthy remain the same. At many institutions across the state, immunologists continue to perform important research that expands knowledge of both bovine and human immunity.

More information about the history of immunology in Texas will be featured in a special exhibit at IMMUNOLOGY 2018™ in Austin.

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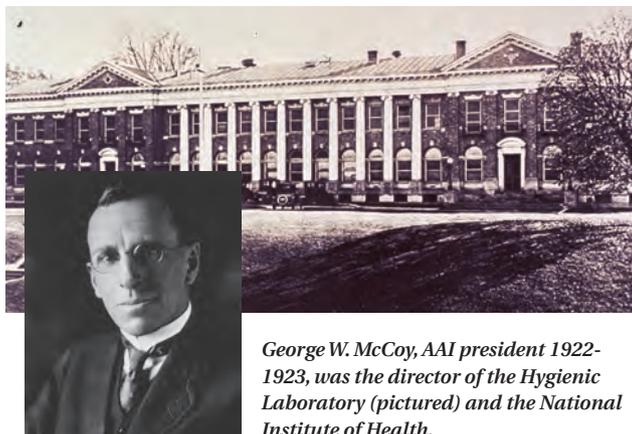
A LEGACY MORE THAN A CENTURY IN THE MAKING

Looking back at AAI and its earliest honorary members

In 1916, The American Association of Immunologists (AAI) welcomed its first honorary members from the Washington, DC, area, initiating a relationship between AAI and the federal biomedical research laboratories of the U.S. Army, Navy, and Public Health Service (PHS), that has endured for over a century.

The seeds of this relationship were planted one year earlier at the second annual meeting of AAI in 1915, held at the Willard Hotel, in the nation's capital. Founding member and AAI Council President A. Parker Hitchens (AAI 1913) proposed to the council a resolution extending “active membership, without the payment of dues” to the directors and assistant directors of the laboratories at the Army Medical School, the Naval Medical School, and the Hygienic Laboratory of the PHS.¹ Hitchens himself had served in a variety of capacities in the U.S. Army Medical Corps and understood the importance of the governmental funding of medical research. By offering these memberships to scientists in these laboratories, AAI could forge important connections and reinforce the importance of a professional society for the growing field. In the context of World War I (1914–1918), this overture to military medical science was also a statement of patriotism and readiness to cooperate for the nation's good.² Hitchens' resolution was unanimously approved.

This declaration made clear that these special memberships were to be associated with director-level positions—not administrators—from these laboratories, suggesting that it was meant to attract working scientists into AAI. During the election of new members at the 1916



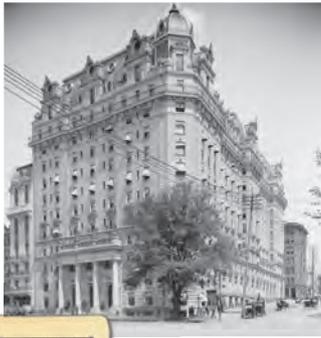
George W. McCoy, AAI president 1922–1923, was the director of the Hygienic Laboratory (pictured) and the National Institute of Health.

annual meeting, no names were read for these new members;³ only when the election was confirmed by the council did their names finally appear in the official record.⁴

With the association only three years old in 1916, membership categories were still a bit fluid; no formalized membership criteria or categories existed. Just

one year later, however, when the first AAI Constitution and Bylaws were enacted, honorary memberships were eliminated. Any honorary memberships prior to the new bylaws were converted to active ones; the idea of non-dues memberships was quietly abandoned.⁵ Because of this, the only people to enjoy this benefit were Edward B. Vedder and Eugene R. Whitmore at the Army Medical School, Edward R. Stitt and Charles S. Butler at the Naval Medical School, and George W. McCoy and Arthur M. Stimson at the Hygienic Laboratory.

Of these former honorary members, McCoy had the most significant involvement with AAI. Just two years after becoming a member, he was elected to the AAI Council and became the ninth AAI president in 1922. During his time as director of the Hygienic Laboratory, the scope of research there grew to encompass basic science, in addition to applied research. In his tenure with the federal



The decision at the AAI annual meeting in 1915 at the Willard Hotel in Washington, DC, initiated the relationship between AAI and federal biomedical laboratories.

government, McCoy presided over the Hygienic Laboratory becoming the National Institute of Health and remained its director until 1937. In that same year, AAI declared McCoy a special honorary member. The dues ledger for McCoy indicates that he was never charged a membership fee throughout his lifelong affiliation with AAI.

The other laboratory directors who had received honorary membership (before the 1917 bylaws) continued their research,

even after leaving the posts that had provided them AAI membership. In addition to being the only honorary member to publish his work in *The Journal of Immunology*, Vedder remained in the Army in various research positions. His efforts gained wider recognition by demonstrating that beriberi was a deficiency disease, and in 1936 he first synthesized thiamine for its treatment.⁶ After retiring from the Army in 1920, Whitmore taught at George Washington and Georgetown universities.⁷ Stitt remained in the Navy, authored two foundational textbooks on bacteriology and tropical disease, served as President Woodrow Wilson's attending physician after his stroke in 1919, and was promoted to surgeon general of the Navy in 1921.⁸ Butler spent his career in the Navy, retiring in 1939.⁹ Stimson spent his entire career in the PHS (1902–1941), serving as the chief of the Division of Scientific Research from 1922–1930.¹⁰

The three institutions that employed these scientists no longer exist as they had in 1915. The growth of government and military research had necessitated their expansion

and relocation to the Maryland suburbs surrounding Washington, DC. After the Hygienic Laboratory became the National Institute of Health under McCoy, the institute relocated to its current Bethesda campus in 1938 and gradually expanded into the National Institutes of Health (NIH) of today. The Army Medical School underwent a few name changes before settling on its identity as the Walter Reed Army Institute of Research and moved its headquarters to its current location in Silver Spring. The Naval Medical School, once located at the Old Naval Observatory in Washington, DC, moved to the new National Naval Medical Center in Bethesda in 1942. As part of the Base Realignment and Closure Commission, on May 13, 2005, the Naval Medical Center became part of the larger Walter Reed National Military Medical Center in Bethesda, across the street from NIH.



The Walter Reed Army Institute for Research traces its beginnings to the laboratories in the U.S. Army Medical School (c. 1916–23).

The scientists employed at these government research institutions have been an active and vital part of AAI since the first honorary memberships were bestowed on its early directors. Today, AAI has the honor of counting more than 220 members from their laboratories. The foresight that Hitchens displayed more than a century earlier laid the groundwork for a long and productive relationship, which has had a profound impact on the study and understanding of immunology.

Attendees at IMMUNOLOGY 2017™ will be able to view a special exhibit highlighting leading members and influential immunology institutions in the Washington, DC, metropolitan area. The History Exhibit will be located on the 2nd floor of the Walter E. Washington Convention Center.

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The AAI Committee on the Status of Women (CSOW): Focusing on the Careers of Women in Immunology

While women have been members of AAI since its founding (Amelia Gates, M.D., and Myrtle Smith, M.D., were charter members in 1913), they represented less than 10 percent of membership until 1958. There wasn't an official group that focused on supporting women immunologists, and addressing career issues unique to them, in the association's first 57 years. In 1970, the AAI Council approved the formation of a five-member Committee on Women's Status. The first committee was chaired by Helene C. Rauch, M.D., Stanford University (AAI '67), and included two other women, Justine S. Garvey, Ph.D., California Institute of Technology (AAI '56) and G. Jeanette Thorbecke, M.D., Ph.D., New York University School of Medicine (AAI '61, president 1989–90).

In 1974, the committee grew to eight members to become the Committee on the Status of Women and Minority Groups. In 1976, the committee was comprised entirely of

women. In 1978, this committee split in two, becoming the Minority Affairs Committee (MAC) and CSOW. The mission of the CSOW was to enhance career opportunities and advance the involvement and recognition of women immunologists within the scientific community.



G. Jeanette Thorbecke
AAI President, 1989-90

In 1992, the CSOW created a forum for discussion about the challenges of being a woman in science by sponsoring its first symposium at the AAI annual meeting held in Anaheim, CA. This “How Far Can Women Succeed in Science?” symposium¹ featured three scientists:

- Susan Leeman, Ph.D., professor, Boston University School of Medicine, *Thoughts Concerning Women in Science*
- Florence P. Haseltine, M.D., Ph.D., director of population research, National Institute of Child Health and Human Development, NIH, *Paying Attention to the Unwritten Rules*
- Phyllis Moen, Ph.D., professor of human development/family studies and sociology, Cornell University, *Women as a Human Resource in Science*

In addition to the committee's interest in career development for women in science, the CSOW has promoted scientific discussion about diseases affecting women. At the 1993 annual meeting in Denver, CO, the CSOW hosted United States Surgeon General M. Jocelyn Elders, M.D, for a keynote lecture on women's health issues. Elders' keynote was followed by a symposium entitled “Modern Women, Modern Plagues: Looking Towards the 21st Century,” which featured scientific talks of “three diseases of particular importance to women,” identified as systemic lupus erythematosus, heterosexual AIDS, and breast cancer.²

The CSOW also highlighted these issues, as well as accomplishments of women immunologists, through a semi-regular feature in the *AAI Newsletter*, “XX-IMMUNO-NOTES-XX.” This feature, which premiered in the September 1993 issue and continued until 2003, sought to “inform all scientists in our organization about the contributions and activities of female Immunologists.”³

The committee found that, although 48.1% of immunology graduate students in 2001 were women, they accounted for just 21.4% of immunology faculty members. In 2016, the percentage of women in immunology faculty positions at these institutions had risen to 29.1% while the representation of women among immunology graduate students held relatively steady at 50.5%.

In 2001, the CSOW conducted a survey examining the percentage of women faculty members within immunology departments or women in immunology graduate programs across 27 institutions in the United States, comparing it to the percentage of women receiving a Ph.D. The committee found that, although 48.1% of immunology graduate students in 2001 were women, they accounted for just 21.4% of immunology faculty members.⁴ The CSOW published these findings in the August 2001 *AAI Newsletter*. A follow-up survey (reprinted on pages 30–33) was conducted in 2016 by the current committee to examine changes in gender equity

over the last 15 years across these same 27 immunology departments and programs. In brief, in 2016, the percentage of women in immunology faculty positions at these institutions had risen to 29.1% while the representation of women among immunology graduate students held relatively steady at 50.5%.⁵

At IMMUNOLOGY 2003™ in Denver, CO, the CSOW hosted a “Careers Lunch,” to “provide an opportunity for aspiring scientists to meet in small groups with leading scientists from academia, industry, and government, to discuss career-related topics.”⁶ The “Careers Lunch” evolved into a co-hosted (with the AAI Education Committee) “Careers in Science Roundtable”, and has been a popular activity at the meeting ever since. This unique career session features a “table leader” expert in a certain topic who answers questions and discusses their topic with up to 8 table participants. Open to graduate students, postdoctoral fellows, and junior faculty, this annual event draws many early-career scientists who are interested in speaking with more experienced scientists on topics related to the work environment (academic research, biotech industry, governmental agencies, non-profits), the transitions from specific career stages, issues in balancing career and family in any career path, and more.

Among its most recent career-development services, in 2013, the CSOW established the Career Advisory Board, which provides early-career scientists and senior postdoctoral fellows an opportunity to obtain guidance from more senior PIs having insight and experience with specific issues.⁷ An online matching process will link the requester with an experienced scientist. Topics include recruiting, grant writing, building networks, balancing family and work, and more. The committee also works to enhance opportunities for women to be selected as speakers and/or chairs at professional meetings and seminar series, or to serve as reviewers, editors, board members, consultants, or in other professional capacities. The CSOW has compiled a Women AAI Member Speaker list of AAI women members who work in immunological research or fulfill leadership roles in non-research careers related to the field.

These CSOW activities have helped to enhance the recognition of women scientists through symposia and presentations, career advice, and surveys assessing the status of women in the field.



Images from the Careers in Science Roundtable at the AAI annual meeting

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1. “Highlights of the 1992 AAI Special Symposium: How Far Can Women Succeed in Science?” *AAI Newsletter*, Summer 1992, 8.
2. “XX-IMMUNO-NOTES-XX: Introduction,” *AAI Newsletter*, September 1993, 6.
3. *Ibid.*
4. AAI Committee on the Status of Women, “XX-IMMUNO-NOTES-XX: Women in Graduate School vs. the Faculty Ranks,” *AAI Newsletter* August 2001, 5–6.
5. Virginia Smith Shapiro et al., “Update on Gender Equity in Immunology, 2001 to 2016,” *The Journal of Immunology* 197, no. 10 (2016): 3751–53.
6. Nancy Hosken, “XX-IMMUNO-NOTES-XX,” *AAI Newsletter*, October–November 2002, 15.
7. For more information on the Career Advisory Board, please visit <http://aai.org/CAB.html>.

As AAI and its members celebrate 100 years of *The Journal of Immunology* (The *Ji*), we're continuing to examine events that had a profound impact on the journal. This article studies the influence that World Wars I and II (WWI/II) had on The *Ji* in its first three decades.

The *Ji* in a World at War

Since its founding in February 1916, *The Ji* has reflected a world outside of the laboratory. Indeed, with an inaugural issue published 18 months into WWI, papers in that first year included research on war-related diseases. With the arrival of WWII, this trend continued more rapidly and in more far-reaching ways, in content and production.

As timely and on point as *The Ji* is today, the same held true yesterday, as well.

WWI: Reshaping a Young AAI

Although the United States stayed out of WWI until April 1917, the fighting had an impact on the formation of *The Ji* and the shape of AAI, which had been founded only a few years earlier, in 1913.

Of the latter, medical service in the military was important enough to AAI leadership that at the second annual meeting in 1915, well before American involvement in the war, AAI extended “active memberships, without the payment of dues” to the directors and assistant directors of the laboratories of the Army Medical School, the Navy Medical School, and the Hygienic Laboratory of the U.S. Public Health Service (renamed the National Institute of Health in 1930).¹

With regard to *The Ji*, the founders envisioned it as an international journal,² but the state of world affairs precluded participation with subscribers, contributors, and editors from the countries of the Central Powers (Germany, Austria-Hungary, Bulgaria, and the Ottoman Empire). By March of 1917, *The Ji*, with 439 subscribers, went to “practically every foreign country,” in Europe except the Central Powers countries.³



World War I recruitment poster, 1917

Arthur N. Edrop, *Library of Congress*

A month later, on April 6, 1917, the U.S. Congress issued a formal declaration of war and plunged the country into the Western Front in Europe. The AAI Council passed a resolution offering the “services of trained bacteriologists and immunologists and the facilities of their respective laboratories” to federal and state government.⁴ Many AAI members, including future presidents and editors of *The Ji*, responded to the call and enlisted in the U.S. Army Medical Reserve Corps (MRC).⁵ So many volunteered that the 1919 annual meeting was very short on abstract submissions. AAI President William H. Park (AAI ’16, president 1918–19) sent a letter to the membership, in which he asked that “all who have had a chance to do experimental work, will feel it a

duty to present a report of this at the annual meeting.”⁶ Nonetheless, only 16 abstracts were presented that year, down from 38 the year before.

Answering the call of duty obviously had an impact on the structure of the AAI Council. When Council member Richard Weil died in the line of duty as a member of the MRC,⁷ his seat was filled by George McCoy, who had been given membership as director of the Hygienic Laboratory of the Public Health Service. In 1918, the first editor-in-chief of *The Ji*, Arthur Coca (AAI ’16, editor-in-chief, *The Ji*, 1916–48, secretary-treasurer 1918–45), was appointed both treasurer pro tem and secretary to replace Willard J. Stone (AAI ’13, treasurer 1913–18) and Martin J. Synnott (AAI ’13, secretary 1913–18), both of whom were serving in the MRC.⁸

1. Minutes of the Second Annual Meeting, May 10, 1915, AAI Archive, Rockville, MD [hereafter AAI-Rockville].

2. James W. Jobling to Simon Flexner, August 5, 1915, Simon Flexner Papers, “Jobling, James W., 1912–1945, Folder 1,” American Philosophical Society, Philadelphia, PA.

3. Letter from Charles Thomas, circulation manager, Williams & Wilkins Co., to Martin J. Synnott, March 30, 1917.

4. Minutes of the Fourth Annual Meeting, April 7, 1917, AAI-Rockville.

5. For more information about AAI members in WWI, see “Immunologists during the First World War: One Soldier-Scientist’s Experience—Stanhope Bayne-Jones,” *AAI Newsletter* (December 2012): 16–23.

6. Letter from William H. Park, to the members of the American Association of Immunologists, 1919, AAI-Rockville.

7. Commissioned into the MRC when the United States entered WWI in 1917, Weil was appointed chief of medical staff at Camp Wheeler near Macon, Georgia. While attending hospitalized troops there, Weil contracted pneumonia and died on November 19, 1917.

8. Minutes of Council Meeting, January 31, 1918.

Immunology on the Battlefields

In his president's address, published in the September 1, 1918, issue of *The JI*, John A. Kolmer (AAI '13, president 1917–18) expressed optimism regarding how the science of immunology would affect the conduct of the war.⁹ He predicted that “a notable victory over the common enemy, disease, will be recorded as one of the greatest triumphs in this greatest of all conflicts” through improvements in sanitation, immunization, and treatment.¹⁰ Immunologists had made advances in combating many diseases that once plagued battlefields, including smallpox, typhoid, tetanus, diphtheria, and syphilis. Typhoid, in particular, was no longer the threat it had once been: as late as 1898, 85 percent of all U.S. deaths in the Spanish-American War were from typhoid, but with mandatory immunization against the disease for all U.S. troops in WWI, the disease claimed only 227 soldiers, *one-quarter of one percent* of all U.S. deaths in the war.¹¹ Kolmer's prediction was proven largely true, as WWI was the first U.S. war in which the death rate from disease was lower than that from battle.¹²

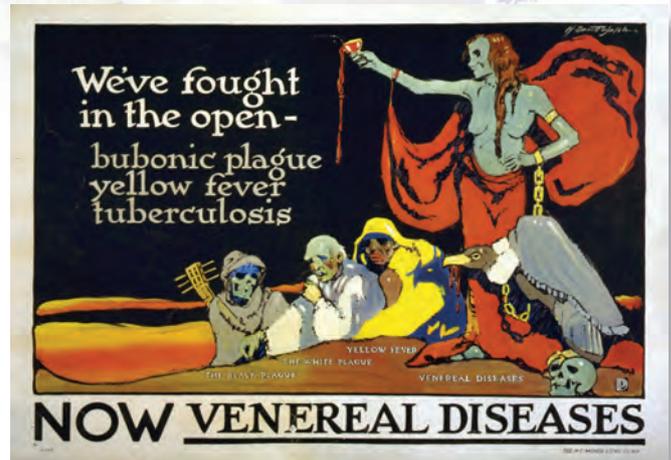
Kolmer also recognized major challenges that could be exacerbated by the war. Most pressing to him were the development of tests for immunity to pneumonia, tuberculosis, and meningococcal meningitis, along with immunizations against measles, anterior

poliomyelitis, syphilis, and gonorrhea.¹³ Tuberculosis and meningitis were among the top wartime killers of American soldiers, although pneumonia overshadowed these two by far, accounting for 83.6 percent of deaths from disease.¹⁴



Typhoid prophylaxis, World War I, c. 1917

Images from the History of Medicine, National Library of Medicine



World War I public health poster, 1918

H. Dewitt Welsh, Library of Congress

Of these 40,000 deaths from pneumonia, 25,000 were attributable to pandemic influenza, a development that Kolmer could not have predicted.

Even before the pandemic of 1918–19, influenza had captured the interest of immunologists. The winter of 1915–16 had seen a sharp increase in the mortality rate from influenza, as an epidemic of the disease swept through most of the nation, killing thousands of people.¹⁵ The mortality rate from influenza in 1916 was 26.4 per 100,000, the highest it had been since 1900.¹⁶ During the pandemic, this ballooned to 400 per 100,000 among American soldiers in the United States in the second week of October 1918 alone. In response to these conditions, *The JI*, in the July 1919 issue, carried three articles focusing on influenza research. All three described experiments with *Bacillus influenzae*, or Pfeiffer's bacillus (now *Haemophilus influenzae*), then suspected to be the cause of influenza rather than an opportunistic pathogen. An article by F. M. Huntoon (AAI '18) and S. Hannum considered both the causal and opportunistic roles and also attempted to understand the relationships between the various strains of influenza “in order to account for the epidemiological features of the pandemic.”¹⁷ *The JI* continued to publish research that sought to address the causes of the pandemic for years after.¹⁸

9. Kolmer's address was delivered at the fifth annual meeting of AAI in Philadelphia, PA, on March 29, 1918.

10. John A. Kolmer, “The Rôle of Immunity in the Conduct of the Present War,” *The Journal of Immunology* 3, no. 5 (September 1, 1918): 371.

11. Leonard P. Ayres, *The War with Germany: A Statistical Summary* (Washington: Government Printing Office, 1919), 125.

12. Ayres, 124.

13. Kolmer, 373–74.

14. Ayres, 126.

15. Jeffrey K. Taubenberger and David M. Morens, “1918 Influenza: The Mother of All Pandemics,” *Emerging Infectious Diseases* 12, no. 1 (2006): 15–22.

16. Department of Commerce, Bureau of the Census, *Mortality Statistics 1916. Seventeenth Annual Report*. (Washington: Government Printing Office, 1918), 38.

17. F. M. Huntoon and S. Hannum, “The Rôle of *Bacillus influenzae* in Clinical Influenza,” *The Journal of Immunology* 4, no. 4 (1919): 168.

18. For more information about the 1918–1919 influenza pandemic in pages of *The JI*, see Mary Litzinger, “The 1918–1919 Influenza Pandemic as Covered in *The Journal of Immunology*,” *AAI Newsletter* (July–August, 2012): 12–13.

Venereal Disease

Another perennial health problem highlighted by the war was sexually transmitted infection. With over four million troops mobilized, the American armed forces needed to educate their personnel on the dangers of venereal disease, specifically syphilis and gonorrhea. Pamphlets published for the War Department contended that because “such diseases as small-pox, yellow fever and typhoid have been practically wiped out...the greatest menace to the country is venereal disease.”¹⁹ From 1916 to 1920, 17 articles on syphilis and various tests for the disease appeared within the pages of *The JI*. Kolmer was especially optimistic about the recent advances in the management of syphilis, as the older mercury-based treatments had largely been replaced with the first chemotherapeutic drug, arsphenamine, also known by its trade name Salvarsan or “compound 606.” This arsenic-based medication was painful to the patient, required more than 18 months of treatment and at least 50 injections, bore unpleasant side effects (such as nausea and vomiting), and had to be stored in sealed vials of nitrogen—but it worked.²⁰



NRA poster, c.1933
Library of Congress

Ikuzo Toyama and Kolmer published an article on their work to explain the mechanisms of both arsphenamine and the older treatment of mercuric chloride. They determined that both drugs worked by increasing antibody production in small doses, whereas massive doses would have the opposite effect.²¹

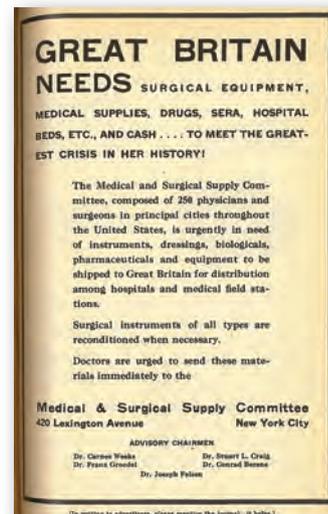
Research on the treatment of syphilis and gonorrhea led to effective public health education campaigns, as was evidenced early on in research concerning the incidence of these diseases among members of the armed forces. Although venereal diseases were still the most frequent cause for soldiers to be out of commission, a study found that, of the 48,167 cases treated at five army camps in the United States in the year ending May 21, 1919, 96 percent had been contracted before the patient enlisted.²² The constant bombardment of soldiers with information about these diseases produced an army with far lower rates of infection than the general public.

Interwar Years

After the Armistice of November 11, 1918, both the United States and the AAI returned to a normal state of affairs. By early 1920, *The JI* had a subscription agent in Berlin to distribute the journal in Germany.²³ In the decades that followed, the economic fortunes of most post-war countries were in a state of flux, but the United States thrived during the Roaring Twenties until Black Tuesday, October 29, 1929, when the stock market crashed, and the Great Depression began.

On June 16, 1933, President Franklin D. Roosevelt established the National Recovery Administration (NRA) as his first large-scale legislative attempt to begin righting the country's economic ship. The goal of the new agency was to bring fair, regulated competition to the market and better working conditions to laborers through the creation of codes to stabilize production; set price controls; and regulate collective bargaining, wages, and maximum work hours for laborers. The NRA emblem, a blue eagle clutching a gear in one talon and lightning bolts in the other, symbolized industry and power. The symbol quickly gained a foothold in the American consciousness and was displayed in shop windows and printed on the packaging of goods to demonstrate support for the agency. Although use of the emblem was voluntary, businesses that did not display or use it were often boycotted.

Scientific publishers were not immune to the public pressure to include the NRA logo on their journals. Thus, the NRA eagle first appeared prominently on the cover of the October 1933 issue of *The JI*.²⁴



Medical and Surgical Supply Committee of America notice, Nov. 1940

The Journal of Immunology

19. American Social Hygiene Association, *Keeping Fit to Fight* (New York, 1918), 3–4.

20. Félix Bosch and Laia Rosich, “The Contributions of Paul Ehrlich to Pharmacology: A Tribute on the Occasion of the Centenary of His Nobel Prize,” *Pharmacology* 82, no. 3 (2008): 177–78.

21. Ikuzo Toyama and John A. Kolmer, “The Influence of Arsphenamine and Mercuric Chlorid upon Complement and Antibody Production,” *The Journal of Immunology* 3, no. 4 (1918): 316.

22. Ayres, 127.

23. “Information for Contributors and Subscribers,” *The Journal of Immunology* 5, no. 1 (1920): 8.

24. “Table of Contents,” *The Journal of Immunology* 25, no. 4 (1933).

WWII: Supporting the Effort

By the late 1930s, immunology had become an established field of research that was both growing and diversifying, and *The JI* was the preeminent journal for immunology in North America. At that time, the journal was publishing one issue each month and nearly 1,000 pages of research each year.

When WWII broke out in Europe in 1939, the first visual clue of the war in *The JI* was a full-page notice from the Medical and Surgical Supply Committee of America in the November 1940 issue. A large, bold headline exclaimed that “Great Britain Needs Surgical Equipment,” in its solicitation of donations of medical supplies from medical professionals and institutions. After the United States entered the war, *The JI* voluntarily and proactively took steps to conserve paper in anticipation of restrictions on supplies. In January 1942, *The JI* published an “Explanation to Subscribers,” explaining the new format of the journal, with smaller type and narrower margins to fit the same amount of content into roughly 20 percent fewer pages.²⁵ In 1943, the War Production Board codified such efforts, issuing regulations limiting publishers to 90 percent of the weight of paper they had used in 1941.²⁶ In early 1944, a “V” logo (“V” for Victory”) appeared on the cover, indicating that the journal was complying with wartime paper restrictions.

Paper wasn’t the only commodity that *The JI* was asked to help conserve. The August 1942 issue included a visually arresting headline over a message from the publisher, Williams and Wilkins: “URGENT: Notice of War Production Board Order Related to Obsolete Plates.” The War Production Board had issued Conservation Order M-99, which required the owners of obsolete printing plates to turn them over so their metals could be used in the war effort.²⁷ Williams and Wilkins had



“Explanation to Subscribers,”
Jan. 1942

The Journal of Immunology

previously provided authors published in *The JI* with the plates used to print their figures. The announcement informed authors that they were subject to “fine or imprisonment” if they did not comply with the government order. Such penalties, however, were likely intended for businesses, not individuals with a single plate here and there.²⁸

The expansion of War Production Board restrictions affected the scientific enterprise more broadly, as travel restrictions caused the cancellation of scientific meetings, including the AAI annual meetings in 1943, 1944, and 1945.

Funding War-Related Research

On June 28, 1941, President Roosevelt issued Executive Order No. 8807 to establish the Office of Scientific Research and Development (OSRD) “for the purpose of assuring adequate provision for research on scientific and medical problems relating to the national defense.”²⁹ This new agency would spend over half a billion dollars on scientific research during the course of the war.

Many contributors to *The JI* benefited from OSRD funding during the war. A total of 23 articles described research funded in whole or in part by OSRD contracts, and the May 1946 issue featured five articles with OSRD funding—one-half of the content for that issue. The OSRD-funded articles in *The JI* reflected the changing needs of the military; the earliest of these articles described research on perennial threats, such as tetanus, typhus, and syphilis, whereas later articles dealt with diseases faced by soldiers fighting in the Pacific, such as dysentery and malaria. These papers were studies in basic research, as well as new and improved diagnostic and treatment options, including vaccine and penicillin research.

Seymour Halbert (AAI ’47), Stuart Mudd (AAI ’27), and Joseph Smolens (AAI ’43) of the University of Pennsylvania published three articles on aspects of Shigella, which had caused several severe outbreaks of dysentery in all theaters of the war.³⁰ Two OSRD-funded articles described methods of producing the *Clostridium perfringens* alpha-toxin, the agent responsible for gas gangrene. Although both incidence and mortality of gas gangrene had declined sharply since WWI, prevention of the debilitating condition remained a priority for

25. The average article length in 1941 was 12.7 pages. With the new format in 1942, the average article length was 10.1 pages.

26. Ernest Kanzlee, “Part 3133—Printing and Publishing: Limitation Order L-241,” *Federal Register* 8 (January 9, 1943): 357.

27. Amory Houghton, “Part 1106—Printing and Publishing: General Conservation Order M-99,” *Federal Register* 7 (August 7, 1942): 6146.

28. The wording of Order M-99, while technically including individuals, was clearly intended to apply to companies, as its primary effect was to compel printers and publishers to certify that they had no obsolete plates in their possession before obtaining new metal.

29. Franklin D. Roosevelt: “Executive Order 8807 Establishing the Office of Scientific Research and Development” (June 28, 1941).

30. S. B. Hays et al., *Preventive Medicine in World War II. Volume IV: Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts* (Washington, D.C.: Office of the Surgeon General, Department of the Army, 1958), 393.

the military.³¹ Michael Heidelberger (AAI '35, president 1946–47, 1948–49) and various co-authors, including Manfred Mayer (AAI '46, president 1976–77), published a series of five articles detailing their unsuccessful quest to find a malaria vaccine. Even with the relative luxury of a large population of volunteer subjects for research and over \$5.5 million spent on malaria research, that goal remained out of reach.³²

At the outset of the war in Europe, penicillin had not yet been used to successfully treat bacterial infections in humans. A few years into the war, however, this changed, and there was an urgent need to understand the antibiotic properties of penicillin and to ramp up production of the new drug. In the United States, the OSRD and pharmaceutical companies were largely responsible for initiating this research.

Although there was only one OSRD-funded paper on penicillin research,³³ the OSRD recommended or supplied penicillin for two other experiments that were published in *The JI*.³⁴ Werner Henle (AAI '38, president 1962–63) and Gertrude Henle focused their research on influenza during WWII from their lab at the University of Chicago; the pair received OSRD contracts for human subject research that resulted in two articles in *The JI*.³⁵

The Army Epidemiological Board

Many contributors to *The JI*, the Henles among them, received wartime funding from the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army (later shortened to the Army Epidemiological Board). At the urging of Brigadier General James S. Simmons, Chief of Preventive Medicine in the Office of the Surgeon General during WWII, and his deputy, Stanhope

Bayne-Jones (AAI '17, president 1930–31), the War Department approved the Board in January 1941 to “prevent catastrophic outbreaks of disease.”³⁶ Influenza was a high priority for the military, as the pandemic during WWI had been one of the largest sources of medical non-battle casualties in the U.S. Army abroad and at home. Among the 17 initial board members and commission directors were nine AAI members, including four past presidents, two future presidents, and six long-time members of *The JI* editorial staff, four of whom were editing the journal throughout the war. Bayne-Jones served as the first administrator of the Board, and Francis G. Blake (AAI '21, president 1934–35) was its first president. Among

the other prominent AAI members and editors of *The JI* who served with the Board were Oswald T. Avery (AAI '20, president 1929–30), Alphonse R. Dochez (AAI '20, president 1931–32), and Thomas Francis, Jr. (AAI '30, president 1949–50). In the next two years, John F. Enders (AAI '36, president 1952–53) joined the Commission on Measles and Mumps, and Karl F. Meyer (AAI '22, president 1940–41) joined the Commission on Tropical Diseases, adding two more active editors of *The JI* to the Board.

Albert Sabin (AAI '46) served on the Board's Commission on Neurotropical Virus Diseases and in 1943, went to Cairo to set up a lab for the study of sandfly fever, infectious hepatitis, and poliomyelitis.³⁷ Sabin was very pleased with the results of his research in the field, especially on sandfly fever, which also shed light on other mosquito-borne diseases, such as dengue.³⁸



Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army, c.1941

Images from the History of Medicine, National Library of Medicine

31. Clinton K. Murray, Mary K. Hinkle, and Heather C. Yun, “History of Infections Associated With Combat-Related Injuries,” *Journal of Trauma Injury, Infection, and Critical Care* 64, Supp. 3 (2008): S226.
32. Michael Heidelberger, Manfred M. Mayer, and Constance R. Demarest, “Studies in Human Malaria I. The Preparation of Vaccines and Suspensions Containing Plasmodia,” *The Journal of Immunology* 52, no. 4 (1946): 325–30.
33. John E. Blair, Miriam Carr, and Joseph Buchman, “The Action of Penicillin on Staphylococci,” *The Journal of Immunology* 52, no. 3 (1946): 281–92.
34. Lowell A. Rantz and William M. M. Kirby, “The Action of Penicillin on the *Staphylococcus* in Vitro,” *The Journal of Immunology* 48, no. 6 (1944): 335–43; Henry Welch, Ruth P. Davis, and Clifford W. Price, “Inhibition of Phagocytosis by Penicillin,” *The Journal of Immunology* 51, no. 1 (1945): 1–4.
35. Werner Henle et al., “Experiments on Vaccination of Human Beings against Epidemic Influenza,” *The Journal of Immunology* 53, no. 1 (1946): 75–93; “Experimental Exposure of Human Subjects to Viruses of Influenza,” *The Journal of Immunology* 52, no. 2 (1946): 145–65.
36. Theodore E. Woodward and Center of Excellence in Military Medical Research and Education, *The Armed Forces Epidemiological Board: Its First Fifty Years* (Falls Church, VA.: Office of the Surgeon General, Department of the Army, 1990), 15.
37. Woodward and Center of Excellence, 57.
38. Letter from Sabin, Albert B., to Riley, William A., dated 1944-04-28, found in Correspondence, General—1943–63—Military Service, Sandfly Fever, Hauck Center for the Albert B. Sabin Archives, Henry R. Winkler Center for the History of the Health Professions, University of Cincinnati, Cincinnati, OH.

Among the many accomplishments of the board were successful treatments or vaccines for pneumonia, influenza, typhoid, typhus, tetanus, diphtheria, and numerous tropical diseases, as well as new understanding of the transferability of cellular immunity and the technique for fluorescent labeling of antibodies. *The JI* was among the journals publishing research produced by the various commissions.



World War II scrap drive poster, c. 1942

Library of Congress

bacteriophages, polio, and the discovery of a new disease. During the war, Mary Hewitt Loveless (AAI '41) completed her influential five-part series, "Immunological Studies of Pollinosis."³⁹ The power of the electron microscope, invented the previous decade, was harnessed to begin the investigation of the processes, mechanisms, and structure of antibodies. Alfred D. Hershey (AAI '42) completed his six-part series on "Specific Precipitation" and multiple papers on phage-antiphage reaction.⁴⁰

Polio remained a disease of constant concern on the homefront during the war. Although no major discoveries regarding polio were made during the war, the research helped set the stage for the post-war breakthroughs. In *The JI*, 12 papers on polio were published with contributions from 12 different authors at seven institutions. The authors included Beatrice F. Howitt; Joseph L. Melnick (AAI '48), a pioneering virologist; and Ulrich Friedemann, a refugee of Nazi Germany. All of the articles were funded by the National Foundation for Infantile Paralysis (commonly known as the March of Dimes), an organization that quickly became a major sponsor of polio treatment and research.⁴¹

In the September 1944 issue, the discovery of the Semliki Forest Virus (SFV) by Kenneth C. Smithburn (AAI '37) and Alexander J. Haddow of the Yellow

Fever Research Institute in Entebbe, Uganda, was published.⁴² Although the discovery of SFV might not have been recognized as a major breakthrough at the time, it has since become a workhorse in immunology. Generally, non-lethal in humans, the virus makes an excellent vector and is used extensively in biological research because it has broad host range and incredibly efficient replication. It is used as a vector to transmit genes encoding vaccines (for viruses of public health interest, such as Chikungunya) and vaccines for cancers that are virally induced. SFV has also been used to treat cancer because it has high anti-tumor properties and therefore, enhances the immune response against solid tumors.

Non-military Research

The JI continued to publish research, independent of the military, on a broad spectrum of topics, including allergic reactions, new technologies,

Wartime Diversity

The JI became a home for a greater diversity of authors and institutions from around the world during the war. It published papers from Jonas Salk (AAI '47) and Alfred Hershey well before they were internationally recognized. Five papers were published to complete a Ph.D. requirement, including that of Abram B. Stavitsky (AAI '50). It published papers from a wide range of institutions, including universities, government facilities, and pharmaceutical companies. Of the 124 articles published during the WWII, 35.9 percent had at least one female author. Manuscripts were accepted from Australia, Brazil, Chile, Egypt, Ireland, Iceland, Israel, Mexico, Sweden, Turkey, and Uganda. *The JI* also published papers from scientists who had fled the Nazi regime, including immunologists Werner and Gertrude Henle, Manfred M. Mayer, Felix Haurowitz (AAI '48), Hilary Koprowski (AAI '46), Ernest Witebsky (AAI '35), and pioneering biomathematician Felix Bernstein.

Faced with changes in research caused by two world wars, *The JI* held true to its mission of publishing peer-reviewed articles at the forefront of immunological research. Following the return to peacetime after WWII, the Cold War would soon begin, and a "Doctor Draft" would affect the research of the next generation of immunologists; this will be explored in the next *AAI Newsletter*.

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Communications and Development;
Daniel S. Patrell, Director of Communications

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

40. Alfred D. Hershey, "Specific Precipitation I-VI," *The Journal of Immunology* 42, no. 4 (1941): 455–84; 42, no. 4 (1941): 485–513; 42, no. 4 (1941): 515–301; 45, no. 1 (1942): 39–50; 46, no. 4 (1943): 249–61; 48, no. 6 (1944): 381–401.

41. Established in 1938, the organization was officially renamed the March of Dimes Birth Defects Foundation in 1976 and March of Dimes Birth Foundation in 2007.

42. Kenneth C. Smithburn and Alexander J. Haddow, "Semliki Forest Virus I. Isolation and Pathologic Properties," *The Journal of Immunology* 49, no. 3 (1944): 141–57. The Yellow Fever Research Institute, Entebbe, Uganda, was supported jointly by the Medical Department of the Uganda Protectorate and the International Health Division of The Rockefeller Foundation.

Scientists and the Doctor Draft: Frank Fitch—The Air Force Years



*Air Force Basic Military Training Graduation Parade, Gunter Air Force Base, Alabama, c. 1955
Courtesy of Frank Fitch*

In a recent interview, AAI member and past president Frank Fitch shared recollections of the military training and service that were components of his early career path in science. The following profile draws on the interview, along with an unpublished Fitch family history and Dr. Fitch's AAI Oral History Project interview of July 18, 2012 (www.aai.org/ohp).



*Frank Fitch, c. 1956
Courtesy of Frank Fitch*

Among the challenges some scientists encountered along the path to a career in research was mandatory military service. For 20 years, spanning the Korean and Vietnam wars, newly minted physicians had to contend with the prospect of being drafted into the armed forces in what became known as the "Doctor Draft." A number of AAI members were required to fulfill their military service away from the lab at military hospitals. Fitch was one of

the many young men who managed both to fulfill their responsibility to their country and maintain a course toward a research or clinical career.

In 1952, President Harry S. Truman signed into law an act establishing the Doctor Draft. Initially intended to bolster the ranks of military personnel during the Korean War, the Doctor Draft remained in place following the war's end in 1953 to maintain medical readiness of the armed services in the event the Cold War became "hot." Following

Frank W. Fitch, M.D., Ph.D., AAI '61, is a professor emeritus of the Department of Pathology, former director of the Ben May Institute, and member of the Committee on Immunology at the University of Chicago. Dr. Fitch was president of The American Association of Immunologists (AAI) from 1992 to 1993 and served as an AAI councillor from 1987 to 1992. He also served as editor-in-chief of The Journal of Immunology from 1997 to 2002. From 1993 to 1994, Fitch served as president of the Federation of American Societies for Experimental Biology (FASEB). During his many years at the University of Chicago, Fitch and members of his lab made important advances in T cell immunology and organ transplantation and the use of monoclonal antibodies and T cell clones in immunology research.

their internship, doctors subject to the Doctor Draft could be inducted for two years of service in the armed forces, potentially disrupting their plans to begin clinical residency or continued education and training toward a research career.

Fitch's father, Harold W. Fitch, was an osteopathic physician in Bushnell, Illinois, who experienced frustration that his degree did not qualify him for full medical licensure. His hope was that his son would follow in his footsteps as an osteopath but only after earning an M.D. so that he could be fully licensed. The younger Fitch, however, after winning an honorable mention in the sixth annual Westinghouse Annual Science Talent Search in high school for describing

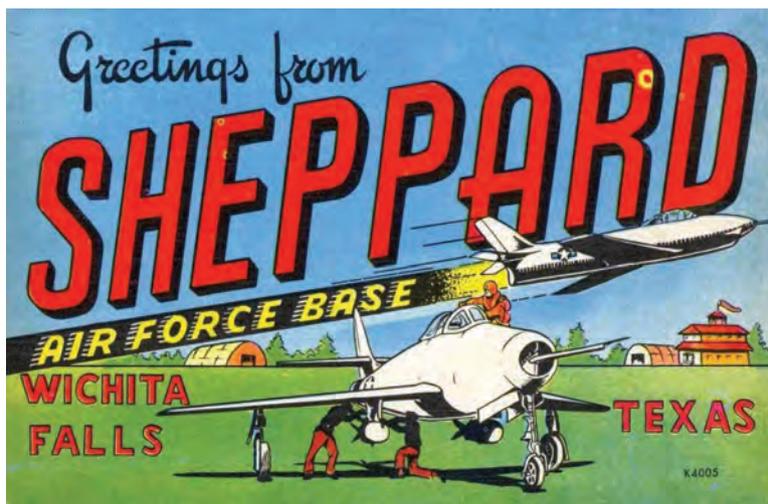


*Frank Fitch, c. 1956
Courtesy of Frank Fitch*

how to build a jet engine, had begun to be “seduced by science itself” and was drawn away from following a clinical path. After completing his pre-med course work in two years, Fitch matriculated at the University of Chicago School of Medicine in January 1950. Early in medical school, Fitch attended a pathology course taught by Robert W. Wissler (AAI '55), who

“emphasized principles over peculiarities.” Fitch decided that research would satisfy his curiosity more than a clinical career. By his last year of medical school, he was serving as a student assistant in that same class and working part time in Wissler's laboratory.

In 1954, the Korean War was over, but the U.S. military remained in a state of heightened readiness for potential new Cold War conflicts. After earning his M.D. from the University of Chicago the previous June, the 25-year-old Fitch had completed a year-long internship emphasizing pathology at the University of Michigan. In April of 1954, he applied for and received a U.S. Public Health Service (USPHS) fellowship to study pathology at the University of Chicago. Shortly after arriving in Chicago that June, however, he received a letter from the McDonough (IL) County Selective Service Board informing him that the end of his internship also brought the end of his military deferment. Fitch now faced a decision.



Frank Fitch served as base doctor at Sheppard Air Force Base 1955 to 1957.

Waiting for his number to be drawn virtually assured being drafted as a private into the U.S. Army and potentially serving as a combat medic were war to break out. Alternatively, Fitch could apply for a commission in a branch of the military offering the opportunity for involvement in research. He chose the latter and applied for, and received, a commission in the U.S. Air Force (USAF) to enter into service later that year with the rank of First Lieutenant.

Fitch applied to the USAF because he believed it was the branch of the military that gave him the greatest possibility to perform pathology research, notably at bases near San Antonio, Texas. At first, prospects looked good because he was assigned a “General Medical Officer-Research” specialty code, although his lack of post-graduate training prevented him from having a pathology designation. Unfortunately, the Air Force at the time had no available opportunities for a General Medical Officer to carry out research.

Making the most of his window before reporting for military training, Fitch began his pathology research at the University of Chicago under his USPHS grant. There he spent the summer researching the effects of lethal total body radiation on hibernating ground squirrels in the Toxicology Laboratory. That autumn Fitch also arranged to enroll as a master's student in pathology at the University of Chicago with tuition support from USPHS going toward completing his degree.

Fitch was officially commissioned as a First Lieutenant Reserve (medical) on September 22, 1954, and was required to report to the Commander of the 382 School Group at Gunter Air Force Base (AFB) for officer training no later than January 31, 1955.

On a cold January day in 1955, Frank and Shirley Fitch packed

up their third-floor walk-up apartment near the University of Chicago campus and made the three-plus-hour drive southwest to Canton, Illinois. Once there, Shirley, the car, and its belongings remained with her parents as her husband boarded a train to Montgomery, Alabama, where he would soon begin Officer Training School at Gunter AFB. From Gunter, the young doctor traveled west to Sheppard

AFB in Wichita Falls, Texas, not far from the Texas-Oklahoma border, to serve the remainder of his commission as a base doctor.

Now joined by Shirley, Fitch arrived at Sheppard AFB—a large aviation training base. The hospital on the base served as a referral center for several bases in Texas and Oklahoma. As he lacked a pathology specialty designation, Fitch was considered a general doctor and assigned to departments as needed.

His first assignment was as Assistant Chief of OB-GYN, a specialty in which he had gained knowledge by way of a two-month rotation during his internship. After a luckily uneventful week of being on call, Fitch received what



Frank and Shirley Fitch
Courtesy of Frank Fitch

would be his permanent assignment on base in the Dependents' Clinic Dispensary, a field of medicine (pediatrics) in which he had limited practical experience.

Fortunately, a seasoned pediatrician was already assigned to the clinic when Fitch arrived. Although the pediatrician's commission ended two months after Fitch's arrival, Fitch "learned more about practical pediatric medicine from him than

in my previous academic settings." Soon thereafter, a newly enlisted doctor with a pediatric specialty designation arrived at the clinic.

Although Fitch was not able to perform bench research during his service as he had hoped, a number of his cases called for study far beyond that required for the average patient. One memorable case involved a four-month-old girl with a goiter caused by a very unusual thyroid abnormality. The base did not have the facilities necessary for the radioactive iodine testing that he needed, but Fitch diagnosed and treated the infant's condition using remote labs.

Fitch spent two years in the Air Force but never once set foot in an airplane. He kept busy on base though. The base doctors often had to deal with domineering senior medical officers who would treat the reserve officers capriciously. One senior pediatrician, in the last two months of his active duty, instituted unreasonable and disruptive procedures in the clinic, demanding that all pediatric cases be referred to him. When Fitch and one of his colleagues refused to follow his rules to the letter, they were "banished" to the enlisted men's dispensary, where they would see up to 100 patients a day.

In Wichita Falls, the Fitches lived more like civilians than career military—their home was off base and Frank did not remain a member of the Officers Club after it was no longer required. They did, however, make friends with other military families and occasionally used base facilities. The biggest event while in Wichita Falls occurred on January 7, 1956, when their first child, Margaret, was born at the base hospital.

At the end of his service in January of 1957, Frank and Shirley were about to head back to Chicago when it suddenly began to snow. It was already late in the day, but the Fitches decided to set off through the snowstorm anyway and "never looked back."

Fitch's time in the Air Force helped convince him that he definitely wanted a career in research rather than clinical practice. Although he had to put aside research for those two years, his military commitment had come at a time when the United States was not at war, and the professional and living conditions at Sheppard AFB were decent.

Even though Fitch did not follow in his father's footsteps and become a practicing physician, the two did find common ground. After 40 years of practice, his father retired and was elected mayor of Bushnell, serving in that capacity from 1969 to 1977. Fitch recollected, "At that time, we had a friendly competition going as to who got the prize this month for getting the most money from the federal government to support our activities—his as mayor and mine as a scientist."

During the years of the Doctor Draft, Fitch and many other AAI members managed to balance their duty to their country with the work they needed to do to launch their research careers. For some, their service was a professional setback, while, for others, it provided them with their first experiences in immunology. Fitch went on to a distinguished career at the University of Chicago,[†] and to years of service to AAI as a member of Council, president, and editor-in-chief of *The Journal of Immunology*. Ultimately, Fitch feels that his time in the Air Force was a reasonable price to pay; he calls it "payback for my other good fortune."

Quotes are from Frank Fitch's AAI Oral History Project interview (www.aai.org/ohp), unpublished family history, and a September 15, 2017, phone interview.

For more information on Frank Fitch and his service to AAI, please visit: www.aai.org/About/History/Past-Presidents-and-Officers/FrankWFitch.

[†] *For information regarding the endowed lectureship honoring Frank W. and Shirley Fitch at the University of Chicago Ben May Laboratory for Cancer Research, see <http://benmay.uchicago.edu/page/fitchlectureship>.*

1916

100 years of *The JI*

2016

Words & Pictures

Advertising in The Journal of Immunology: The First 50 Years

Early editions of *The Journal of Immunology* (*The JI*) with their simple text-based covers paled in comparison with the visually impressive covers of the journal of today. The entire first volume in 1916 contained only a single use of photographic images—a series of five photographs showing kidney lesions resulting from chronic anaphylaxis.¹ All of this changed, of course, with the arrival of the first ads, which drew the reader from text to eye-catching, graphic elements meant to induce purchases. Looking back on decades of ads published in *The JI*, we see that they illustrate a fascinating history of the journal and the field: what advertisers thought would interest early scientists and how ads changed to address the needs of immunology's maturing, diversifying, and expanding discipline.

Ads in the first 50 years of *The JI* fall into four general categories according to their specific appeals or styles. The largest group of ads promoted the tools necessary to perform research, such as lab equipment, research animals, and reagents, with the drugs and other pharmaceutical products comprising a second category. A third type of ad publicized civic engagement campaigns that would be of interest to scientists. A fourth category emerged when journal advertisers began using modern graphic design and advertising techniques to strengthen their message. The following advertisements (Figures 1-4) are examples of each of these categories.

**MANDLER DIATOMACEOUS FILTERS
FOR BACTERIOLOGICAL WORK**

No. 27689. Mandler Diatomaceous Filter Cylinders with Metallic Headpieces

Cross section showing Mandler Diatomaceous Filter attached to glass mantle in correct position for filtering

Mandler Diatomaceous Filters are specially made for the filtering of serums, toxins and other sterile liquids of all sorts. The Infusorial Products Company, of Toledo, have been experimenting since 1914 toward the perfection of diatomaceous earth filters for bacteriological laboratory use in connection with their manufacture of filters for household and manufacturing purposes. With the assistance and cooperation of bacteriologists in the laboratories of several of the largest manufacturers of biological products, U. S. Government Departments, etc., a filtering mass has now been perfected which seems likely to surpass in quality that heretofore used for similar purposes.

The metal caps are of heavy brass nickel plated and provided with a new feature in the way of a special projection fitting inside the tube, which prevents the cap from working back and forth with a tendency to destroy the cement joint. The cementing of the cylinder to the metal cap is a distinct improvement over the method heretofore followed. With the exception of a new size, 8 x 1½ inches, the cylinders offered correspond exactly in size and may be used in the same fittings as the filters of foreign make heretofore widely used for similar purposes.

27689. Filters, Mandler Diatomaceous, cylinders only, with metallic headpieces, with certificate of air pressure test.

Size, inches.....	10x2	8x1½	8x1	5x1	2½x½	1½x½
Each, net.....	3.50	3.15	3.00	2.50	1.25	1.15

27690. Filters, Mandler Diatomaceous, with glass mantle with circular opening in bottom as shown in illustration, but without flask or other container for filtering.

Size of cylinder, inches.....	10x2	8x1½	8x1	5x1	2½x½	1½x½
Each, net.....	5.25	4.40	4.25	3.50	2.00	1.65

27691. Glass Mantles only, for Mandler Diatomaceous Filters, such as are included with No. 27690.

Size, inches.....	14x4	11x2½	5½x2½	4x1	2½x½
Each, net.....	1.75	1.25	1.00	.75	.50

ARTHUR H. THOMAS COMPANY
IMPORTERS—DEALERS—EXPORTERS
LABORATORY APPARATUS AND REAGENTS
WEST WASHINGTON SQUARE PHILADELPHIA, U.S.A.

Figure 1: Mandler Diatomaceous Filters, 1919
The Journal of Immunology

¹ T. Harris Boughton, "Kidney Lesions in Chronic Anaphylaxis," *The Journal of Immunology* 1, no. 1 (1916):105–18

Tools for Immunology Research

Ads comprising the broadest of the four categories focused on tools of immunological research: equipment, literature (scientific and medical journals and books), research animals, and reagents. Perhaps the finest example in this category is the first advertisement ever to appear in *The JI*. The Arthur H. Thomas Company promoted its Mandler diatomaceous filters (Figure 1) in the first ad ever placed in the journal (December 1916²). It stands as an example of the instructive nature of early advertising for tools used in immunological research. The ad includes a detailed rendering and a technical description of the uses and composition of the filter, as well as pricing. More discursive than most ads today, the description of the filter was written at a college reading level as was appropriate for readers of *The JI*, most of whom were M.D.s in 1916. The advanced level of writing highlights the cooperation between bacteriologists in industry and the U.S. government in perfecting the filter.

The Mandler filter, itself a new product on the market in 1916, was novel also for being designed and built in the United States. At the time, many American manufacturers of laboratory equipment were copying European designs. American production of such equipment arose with the growth of laboratory research in the U.S. prior to the outbreak of the World War I. Arthur H. Thomas Company, founded in 1900 in Philadelphia, was an early supplier of domestic and European laboratory products to the American market. When, in 1914, the company redesigned its catalog with illustrations and detailed

THE JOURNAL OF IMMUNOLOGY 1



Save the Tenth Child

STATISTICAL data show that approximately 10% of all children having Diphtheria die. Early and adequate Antitoxin treatment would save these children. In meeting this grave responsibility are you sure that your little patients are receiving the best Antitoxin obtainable? Do you have a satisfying consciousness of having done for them all that can be done?

The use of Parke, Davis & Company's Antitoxin inspires just that sort of confidence. For a quarter of a century it has been recognized as the standard the world over. It is potent, pure, and concentrated.

Parke, Davis & Company's Antitoxin is produced in a laboratory possessing unsurpassed facilities. Excellence in achievement here dominates all other interests.

"DIPHThERIA IMMUNIZATION." a reprint, sent on request. Write nearest branch: Detroit, New York, Chicago, Kansas City, Baltimore, New Orleans, St. Louis, Minneapolis, or Seattle.

Parke, Davis & Company

Figure 2: Save the Tenth Child, 1922
The Journal of Immunology

² Research yielded no ads in *The JI* prior to volume 2, issue 1, in December 1916.

descriptions, such as seen in Figure 1, the catalog emerged as the “bible” of the U.S. laboratory research industry. Arthur H. Thomas Company was renamed Thomas Scientific in 1983 and continues to sell equipment and supplies to the scientific community today.

Products of Immunology Research

Some of the largest U.S. pharmaceutical companies of their day advertised their products in *The JI*, including Parke-Davis & Company, H. K. Mulford Company, The Arlington Chemical Company, and Wyeth.³ These and other companies promoted drugs and other pharmaceutical products.

Ads for these pharmaceutical products (for treating diseases and allergies) were present in almost every issue of *The JI* through World War II. These included treatments, antitoxins, and vaccines for maladies such as hay fever, poison ivy, pertussis, tuberculosis, scarlet fever, influenza, and diphtheria.

The “Save the Tenth Child” advertisement (Figure 2) is notable as one of the few that attempted to sell a pharmaceutical product to clinicians through a combination of fact and fear. The ad, which appeared only once in *The JI* (December 1922), called attention to diphtheria, still a deadly disease. In the previous year, there were 206,000 cases, with 15,520 deaths (7.5 percent mortality rate). Even with the availability of diphtheria antitoxins for over two decades and an easy and reliable diagnostic test for the disease (the Schick test), the mortality rate among children at the time was typically higher, up to 20 percent.

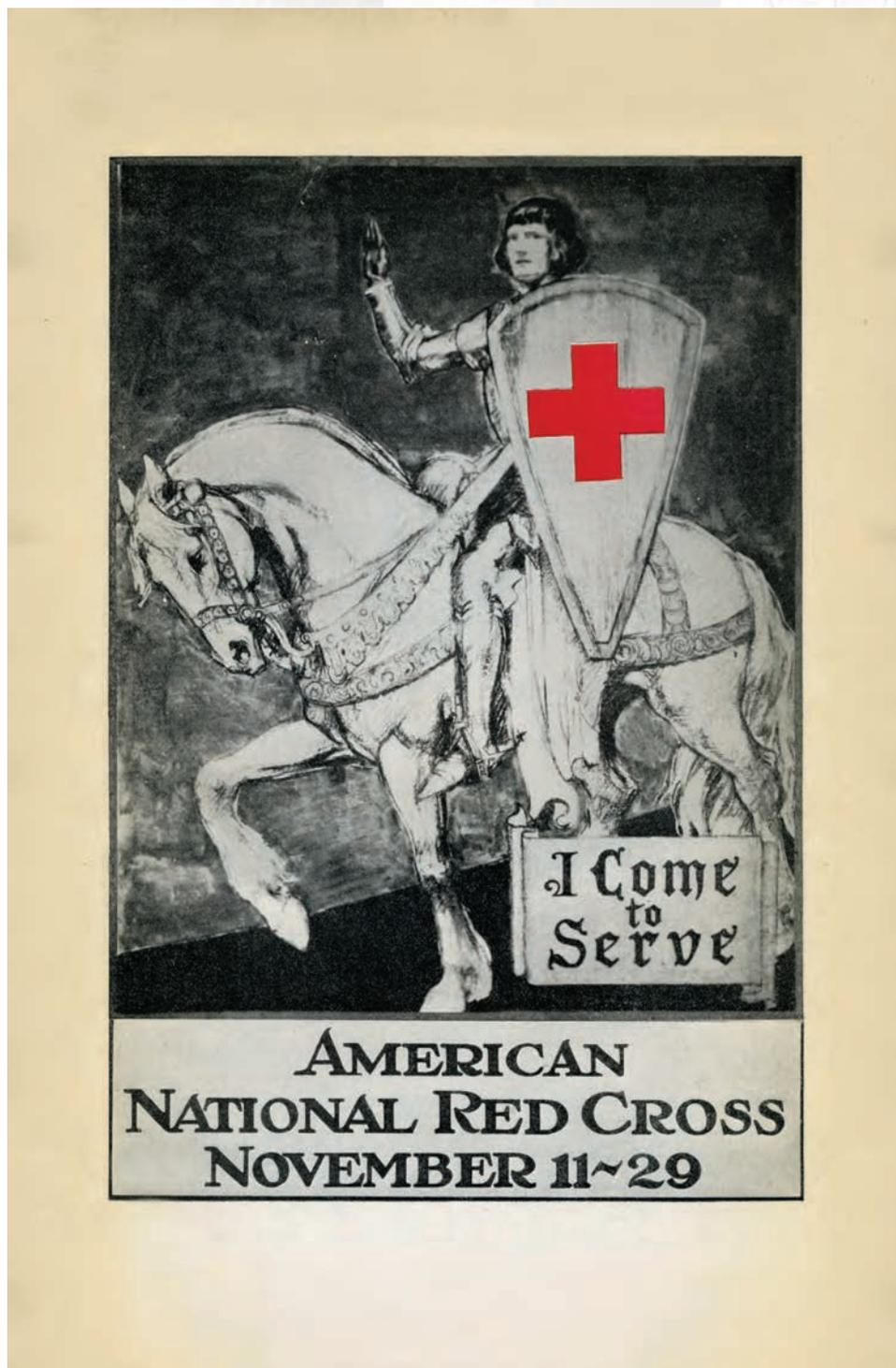


Figure 3: American National Red Cross Roll Call, 1923
The Journal of Immunology

³ Parke-Davis was acquired by Pfizer in 2000. Mulford merged with Sharp and Dohme in 1929 and later with Merck & Co. in 1953. The Arlington Chemical Company was acquired by the U.S. Vitamin and Pharmaceutical Corporation in 1951 and later bought by Revlon in 1966. Wyeth was acquired by Pfizer in 2009.

In 1890, Emil von Behring announced that he had created a successful diphtheria antitoxin. The following year, George Davis (“Davis” in Parke-Davis) recruited scientists from the University of Michigan, including E. M. Houghton (AAI '16). They set up a lab and developed the Parke-Davis antitoxin.⁴ By the early 1920s there were many antitoxins commercially available for clinicians to select. In this case Parke-Davis appealed to the readers’ sense of responsibility to their “little patients”—not only the responsibility to treat them effectively but also to use the “best Antitoxin available.” Without mentioning the cases of deaths from antitoxin treatment, which were rare but newsworthy, the ad implies that the Parke-Davis antitoxin, produced “in a laboratory possessing unsurpassed facilities,” would be safer than its competitors’. In the environment exemplified by the Pure Food and Drug Act of 1906, this appeal to purity and high scientific standards was particularly attractive.

Civic Engagement Campaigns

Civic engagement campaigns appeared exclusively in the first three decades of the journal with ads promoting involvement in issues of public concern or public health crusades.

In November 1923, the first civic engagement campaign advertisement appeared in the final issue of the year. It would have been striking to any reader of the journal because of the first use of color ink in *The JI*. The ad (Figure 3) is for the seventh annual American National Red Cross Roll Call in 1923, which lasted

124 products for tissue culture procedures

CULTURSTAT—sterile, lyophilized tissue culture media/ sterile animal sera/ sterile embryo extracts and serum/ liquid and dry tissue culture media and reagents/ cell cultures, primary and serially propagated/ B-B-L media for pleuropneumonia-like organisms/ FALCON tissue culture dishes, flasks, tubes/ FALCON plastic pipet

Aardvarks* we don't have

BUT VIRTUALLY ANYTHING ELSE YOU MIGHT NEED FOR TISSUE CULTURE PROCEDURES WE CAN SUPPLY. For example, horse, calf, fetal calf, rabbit, chicken, swine, human, and lamb are only some of the sterile animal sera available. One hundred and twenty-four different products in 323 different package forms are ready to meet your specific requirements.

CULTURSTAT—sterile, lyophilized tissue culture media—is ready to use in seconds, offers added convenience and saves time for the busy researcher.

Products of B-D Laboratories are available through your local distributor. Further information on request.

B-D
B-D LABORATORIES INC., BALTIMORE, MARYLAND, U.S.A.

BBI Baltimore Biological Laboratory
Falcon Plastics
Science Education Products

In Canada: Becton, Dickinson, & Co., Canada, Ltd., Clarkson, Ontario
Overseas: Becton, Dickinson & Co., S.A., P.O. Box 1173, Colon, Free Zone, Panama

B-D, B-B-L, CULTURSTAT, FALCON, AND SEPCO ARE TRADEMARKS. 04964

Figure 4: Aardvarks We Don't Have, 1955
The Journal of Immunology

⁴ Milton L. Hoejze, "The Early History of Parke-Davis and Company," *Bulletin of the History of Chemistry* 25, no. 1 (2000): 31–32

from Armistice Day, November 11, to Thanksgiving, November 29. This annual fundraising drive recruited new volunteers and brought in a significant portion of the more than \$10 million the Red Cross spent each year.

This ad was rather unusual compared with most American Red Cross ads of the early 1920s. Ads at that time typically featured images of Red Cross nurses promoting the organization's non-militant activities, including public health nursing services in rural areas, disaster preparedness, and the Junior Red Cross. Although the First World War had ended five years before on November 11, 1918, the Red Cross of the early 1920s was an organization in transition. After receiving accolades during the war, it entered peacetime turmoil as the Red Cross faced plummeting membership, declining dues, a reorganization of the national office, and public critiques of wartime management and finances. Despite these challenges, the organization remained steadfast to its commitments, including the growing financial burden of being a primary provider of treatment and benefits for disabled veterans and their families.⁵

Although having no bearing on research, the appeal and accompanying artwork would have resonated deeply with members of the American Association of Immunologists (AAI) and readers of *The JI*.⁶

Following an AAI resolution in April 1917 offering the "services and facilities" of member laboratories to the "Federal and respective State governments" to satisfy the need for "bacteriologists and immunologists" for the war effort, a significant number of AAI members and *The JI* editors had become directly involved in the war.⁷ Some volunteered in the U.S. Army Medical Corp and served in hospitals or on the front lines in Europe. Others who enlisted remained in the states conducting wartime research at their laboratories.⁸ The wartime experiences of AAI members would have made them promising candidates for participation in the Roll Call.

Modern Advertising

As the birth of modern advertising started to "animate the inanimate," using eye-catching color printing and photography, journal ads began appealing to the reader through visual creativity as well as a compelling "story."

Modern advertising came a little later to *The JI* than to commercial publications, but the 1950s brought contemporary design and advertising techniques to the advertisements published in the journal. The ads were no longer plainly factual. Text was simplified and abbreviated, and most ads featured new design and fonts, photography, color, trademarks, and/or slogans.

Becton, Dickinson and Company (BD) stood apart as one of the most innovative advertisers (Figure 4), especially in the use of color ads. BD had recently expanded beyond designing and manufacturing medical equipment with its acquisition of Baltimore Biological Laboratory in 1955. BD Laboratories quickly became a significant source of the reagents so important to immunological research and began promoting their products such as the one featured in the ad on the previous page.

This particular ad uses a contemporary approach in both design and copy to sell specialized biological research materials to scientists in the same way that consumer goods were sold to the public.⁹ The whimsical language and design appealed to modern sensibilities, but the ad still informed the readers about what BD could offer. It focused on the wide variety of products: 124 products in 323 package forms, which reflect both the diversity of tools and expanding need of new reagents being used by researchers.

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

Contributors: Kaylene J. Kenyon, Ph.D., AAI Publication Director; Charles Richter, AAI History Intern

Editors: Mary I. Bradshaw, AAI Senior Director of Communications and Development; Daniel S. Patrell, AAI Director of Communications

⁵ For a more detailed assessment of the American Red Cross from 1918 to 1923, see Foster Rhea Dulles, *The American Red Cross: A History* (New York: Harper & Brothers, 1950), 148–256; Patrick F. Gilbo, *The American Red Cross: The First Century* (New York: HarperCollins, 1981), 95–96.

⁶ Dulles, *The American Red Cross*, 221.

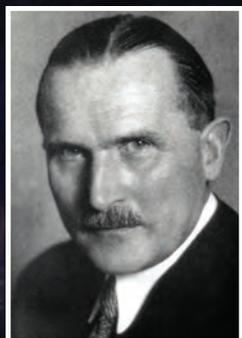
⁷ "Minutes of the Fourth Annual Meeting of the American Association of Immunologists," April 6–7, 1917, AAI Archive, Rockville, Maryland.

⁸ Those who enlisted included AAI member Richard Weil, AAI president (1916–17), member of *The JI* board of editors (1916–1917), and author of the first article in the journal, who volunteered for the U.S. Army Medical Corp and died of complications from the 1917 influenza pandemic while stationed at Camp Wheeler, Georgia.

⁹ Note the asterisk after the slogan refers to the crossed-out picture of an aardvark below. The image is labelled "This is an aardvark." Most casual references to the animal in newspapers at the time included a basic description.

FEATURE:
AAI PROFILES
IN LEADERSHIP

Karl F. Meyer: The Renaissance Immunologist



Karl F. Meyer, c. 1940
AAI Collection, Center for Biological
Sciences Archive, UMBC



Hooper Foundation mural (detail), University of California, San Francisco, by Bernard Zakheim
University of California, San Francisco, Special Collections

In a career spanning 65 years and three continents, Karl F. Meyer (AAI 1922, president 1940–41), known as “K.F.” to his colleagues, was a true renaissance immunologist. He not only made numerous advances in the understanding of human and animal diseases, but also introduced revolutionary theories of disease transmission and successfully straddled the academy-industry line. He established the Department of Bacteriology at the University of California, San Francisco (UCSF), where he worked for over 60 years. His legacy of research, teaching, and service seems almost too great for one scientist.

EDUCATION

Meyer was born in Basel, Switzerland, in 1884. His interest in pathology began in childhood, when his biology teacher brought fish with tumors or other anomalies to class for the students to examine. Young Karl was captivated by the possibility of looking at the specimen under a microscope and seeing a parasite that may have been the cause of the malformation.¹ The role of parasites in disease



Ernst Leitz microscope, c. 1894
National Museum of American
History

was just beginning to be understood—Charles Louis Alphonse Laveran had first observed the malaria parasite with a microscope in 1880—so Meyer was experiencing a scientific revolution right in his classroom.

At the age of 18, Meyer enrolled at the University of Basel and, after one semester, transferred to the University of Zurich because of its

renowned comparative anatomy department. He excelled in his studies there, passing first qualifying examinations in zoology, botany, physics, and chemistry with flying colors.



Zurich (between 1890 and 1900)
Library of Congress

Because of his interest in tissue sectioning and microscopic structure, one of Meyer’s professors recommended that he study under Heinrich Zangger, a professor of physiology at the university’s veterinary school.²

Meyer considered his move to the veterinary school to be the true beginning of his career. There, he was able to immerse himself in human and animal physiology and biochemistry. His second qualifying examinations were in anatomy, physiology, biochemistry, and histology, and led to his graduate study.³

Arriving at the University of Bern for his doctoral thesis work in 1906, Meyer wanted to work in the laboratory of Theodor Langhans but was initially rebuffed by the eminent German pathologist. Two days later, while Langhans was performing an autopsy, Meyer decided to surreptitiously remove a sample of a jaw tumor from the cadaver, pickle it, and create sections in which he found liver cells. He took the slides to Langhans, who—without knowing where they came from—agreed with Meyer’s diagnosis of a teratoma. When Meyer told him where he had acquired the sample, Langhans was so impressed by the speed and quality of the sections that he hired him on the spot for his lab.⁴

Because of the oddities in the Swiss university system and Meyer’s diverse work with many advisors, his D.V.M. was awarded by the University of Zurich in 1909 even though he did none of his actual graduate work there.

EARLY CAREER

Soon after receiving his doctorate, Meyer went to work in South Africa with the Swiss veterinarian Arnold Theiler. He intended to assist in the manufacture of rabies vaccine for local use at the Onderstepoort Veterinary Research

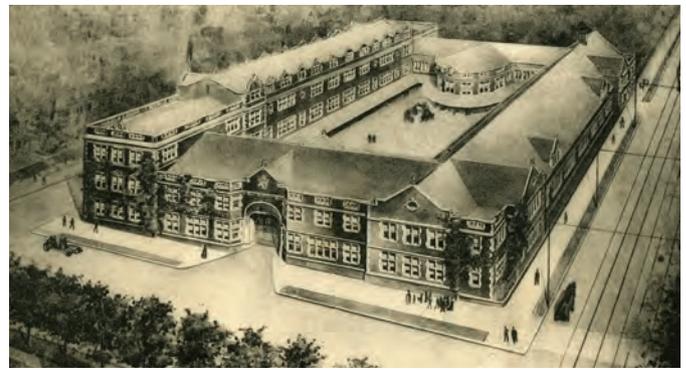


Sir Arnold Theiler
National Library of Medicine

Institute. His duties quickly multiplied there and he eventually butted heads with Theiler, founder of Onderstepoort and pillar of veterinary sciences in the country. They disagreed whether African East Coast Fever (theileriosis) could be transmitted in the absence of ticks. When Meyer successfully demonstrated both transmission and possible immunization of the disease

through tissue transplants, contrary to Theiler’s previously published research, Theiler demanded that the results be published under his name as the director of the institute. Meyer refused, and the two never spoke directly to one another again.⁵ Eventually, Theiler had to admit that he had been wrong, but Meyer was long gone from Africa by that time.⁶

In 1910, Meyer came to the United States when he accepted the position of assistant professor of pathology at the University of Pennsylvania. Although the intellectual community of Philadelphia welcomed him, he later recalled finding his students at Penn disappointing, and constantly feeling like an outsider at the university. But his experiences in South Africa garnered him invitations to join the Pennsylvania Livestock Sanitary Board and the Philadelphia Milk Commission; both provided satisfying



Veterinary Medicine Building, c. 1910
University of Pennsylvania, University Archives

and familiar challenges. His experiences with these industry-related organizations would prepare him for a long legacy of consultation to ensure food safety.⁷

In these first few years in the United States, Meyer also had opportunities to meet many of the giants of early immunology at Penn and at scientific meetings, including John A. Kolmer (AAI 1913, president 1917–18), Victor C. Vaughan (AAI 1915), and Theobald Smith (AAI 1920). They helped convince him that the United States was “worth staying around for.”⁸

Then in early 1913 a new opportunity arose. Meyer went for lunch with his colleague at Penn, Richard M. Pierce, who immediately told him, “You’re going to California.” Not only did Pierce have a lead on a job working with Frederick P. Gay (AAI 1918, president 1921–22) at the University of California, Berkeley, but he had also heard about the enormous grant from the Hooper family to establish an institute of medical research at UCSF, which Pierce believed could become “the Rockefeller Institute of the West.”⁹

Meyer was initially skeptical about moving to California, but he took the job at Berkeley and, in 1915, also joined the faculty at the newly established Hooper Foundation at UCSF. This was the first medical research foundation in the United States to be incorporated as a university department and he became its second director in 1921. After crossing



Hooper Foundation staff (1915–16), Meyer front row, second from right
University of California, San Francisco, University Archives

the equator twice, the Atlantic Ocean and the United States once, and countless time zones, Meyer finally found a permanent home in the Golden State, where he remained affiliated with both Berkeley and UCSF in various capacities for the rest of his life.

In California, Meyer found the freedom he had long sought to explore his many immunological interests. He could investigate a particular topic, move on to another problem, and return to the original matter with new insights. Over his long career one constant was his drive to understand how diseases could lie dormant and unnoticed for years before producing a sudden outbreak. His work on disease cycles led him to introduce a new concept: reservoirs of disease. This line of thinking was instrumental in fighting plague in the American West and also helped him develop effective methods to ensure food safety across multiple industries.

LATENT INFECTIONS AND RESERVOIRS OF DISEASE

The myriad diseases that Meyer studied led him to reconsider the basic relationship between humans, animals, and pathogens. He argued that it was wrong to approach infections “from the standpoint, not of the agent, but of the altered state of the host—the disease.”¹⁰ The ability to identify subclinical infections had proven this approach untenable. Instead, by the 1930s, Meyer wanted to base disease research on the “biologic definition of an infection as a host-parasite relationship.”¹¹ A notorious tainted spaghetti casserole incident two decades earlier helped lead Meyer toward this way of thinking about disease.

In the days following a 1914 church dinner in Hanford, California, 93 people who had eaten food from the dinner contracted typhoid fever.¹² Meyer was part of the team led by Wilbur A. Sawyer, director of the Hygienic Laboratory of the California State Board of Health, that investigated the cause of the outbreak. By interviewing the typhoid patients in the growing San Joaquin Valley town about the dishes they had sampled and cross-checking against the menu, it was determined that the culprit was a baked spaghetti dish.

Among those who participated in preparing the dish was a boarding-house operator whose medical history suggested she was likely a typhoid carrier. By preparing replica casseroles inoculated with typhoid, Sawyer showed that it would have been impossible for the spaghetti to have

been heated sufficiently to kill the typhoid bacteria. When Meyer dug into the story, he felt it was emblematic of “a lack of social consciousness” that pushed him to advocate for public health and preventive medicine.¹³ To do this, he would have to understand why some infections remained latent but transmissible.

A recollection from his early days in Zurich at the turn of the century provided some insight: in the autopsy room, 98 percent of people who died from causes other than tuberculosis nevertheless had tubercle lesions, leading Meyer to call the population “tuberculinized.”¹⁴ In the early 1920s, Meyer and his colleagues started to think about infection from the perspective of a parasitologist, noticing that “when you had a roundworm or flatworm infection, you frequently didn’t show any symptoms at all.”¹⁵ By 1928, he was in the practice of referring to bacteria and viruses as “parasites” and considering “the ability of the animal or the man to accept this parasite” as a critical element in the transition from infection to disease.¹⁶

Around 1930, an abnormally high incidence of tularemia infection among people bitten by dogs in Sonoma County caught his attention, and he soon had a eureka moment.

Although the dogs showed no clinical signs of the disease, upon examination, they were found to have produced antibodies against the bacterium. The dogs were latent carriers, transmitting tularemia from a larger reservoir of infected rabbits to unfortunate humans.¹⁷

In his 1931 Ludvig Hektoen Lecture, Meyer articulated the theory of the animal kingdom

as a reservoir of disease and hoped that this model would lead to novel approaches for dealing with emerging zoonoses. Eventually, he catalogued dozens of diseases by their specific animal carrier paths, allowing him to recommend likely strategies for diagnosis and elimination, including destruction of infected animals, vaccination where possible, or abatement of insect vectors.¹⁸

PUBLIC HEALTH AND SAVING INDUSTRIES

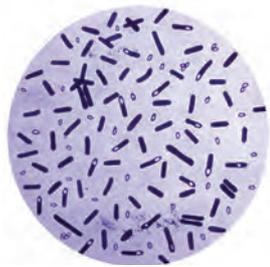
Throughout his career, Meyer worked with various food industries to improve food safety, sometimes saving them from complete ruin. Very soon after arriving in San Francisco, he questioned the testing methods for bovine tuberculosis and arranged with the San Francisco Milk



*Typhoid fever spaghetti casserole article, July 11, 1915
Richmond Times-Dispatch*

Commission to test the milk supply. He discovered that none of the certified milk carried tuberculosis, but “all the first-class milk in San Francisco was infected with *Brucella*.”¹⁹

This finding led to extensive study on the pathogenicity of *Brucella*, especially in infants. In the course of the milk investigations, one dairy was found to be producing milk contaminated with human streptococci, which was causing septic sore-throat epidemics. Meyer’s team cultured every worker in the dairy, and if they found one infected with hemolytic streptococci, the worker had a choice: “he was either discharged, or at the expense of the Milk Commission, he was tonsillectomized.”²⁰



Clostridium botulinum and bacterial endospores
CDC

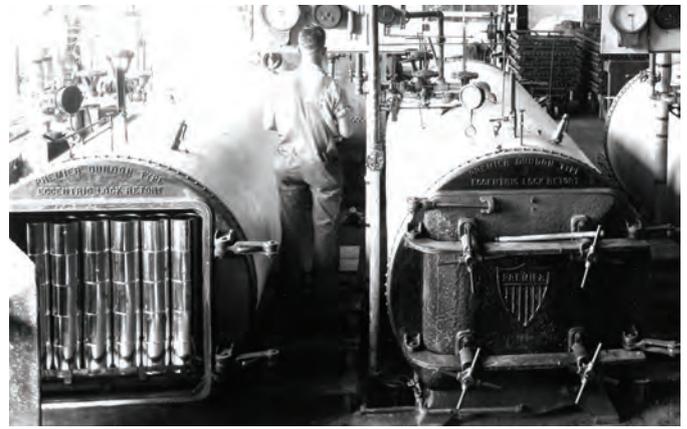
In 1919, Meyer was brought in to advise an informal consortium of California’s largest canning companies on the problem of botulism in canned food, as he had taught courses on anaerobic infections during the First World War.²¹ Tainted California olives had caused deaths in the Midwest, leading to quarantines on all California canned goods

in Michigan and Ohio. Some canners were ready to stop canning olives altogether. Meyer, recognizing that the canners did not have a scientifically sound method for food sterilization, exploded at this proposed solution:

*Absolutely not! Because your whole canning procedure is empiricism. I can just visualize what happens. You figure on the cuff of your shirt the time and temperature which you think is necessary to sterilize the product. Then you put it in a retort which is not controlled. After having given it a cook for such-and-such a time it goes in the warehouse, and if it doesn’t blow up in the next forty-eight hours, this thing is safe.*²²

Convinced that Meyer could provide an effective research plan to eliminate botulism, the director of the National Canners Association asked him to present the canners with a budget the next morning. Meyer and Ernest Dickson of Stanford sat down at the Pig’n Whistle restaurant in downtown San Francisco and worked out an annual budget over tea. When Meyer tabulated it at \$30,000,²³ Dickson slumped in his seat, thinking the canners would never underwrite such an amount. ²⁴ Nevertheless, Meyer took the budget to the meeting with the canners.

R. I. Bentley, president of the California Packing Corporation, pointed out that his company alone was losing \$70,000 a week under the Midwest quarantines, so the research proposal was easily justified. Even in 1919, canning was a multi-billion dollar industry.



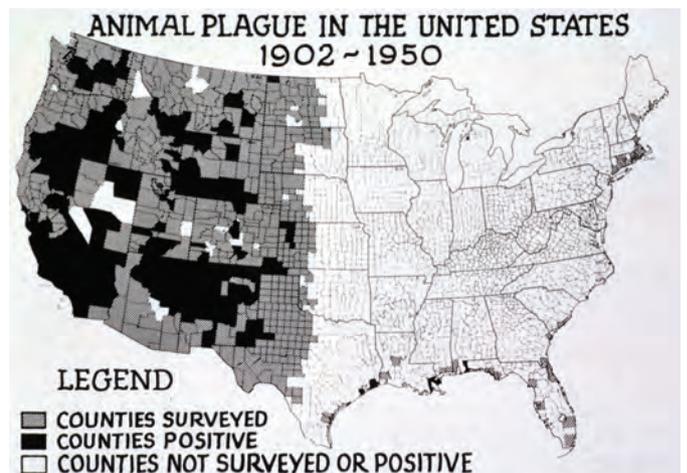
Cannery worker inspecting battery of retorts, c. 1920
San Jose State University Special Collections & Archives

Over the next three years, Meyer developed techniques for testing and sterilizing canned foods that would reliably neutralize any *Clostridium botulinum* spores without destroying the food itself. Later in life, he joked that he had become “one of the most fantastic parasites” on the big canning companies—a parasite that they could not live without.²⁵

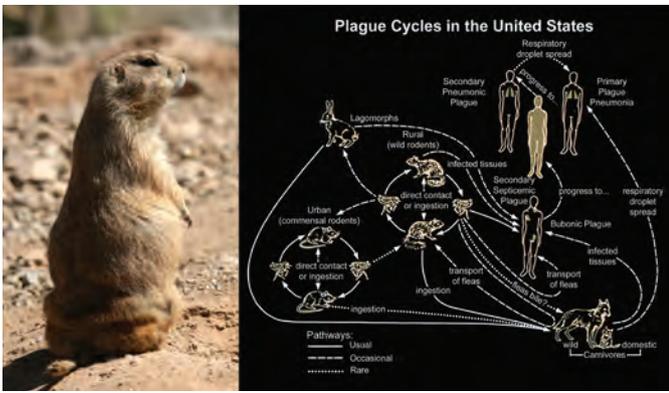
PLAGUE

Plague, in all its manifestations, had fascinated Meyer ever since his time in Africa, where he saw cases of the disease firsthand.²⁶ When he arrived in San Francisco, the city had recently experienced a number of outbreaks spread by rats around the port. These included a nearly four-year (1900–1904) bubonic plague epidemic centered in the Chinatown section, and another following the 1906 earthquake.

In the rural areas far from the port, however, reports of plague posed a medical mystery in that they contradicted the current medical theories on the transmission of the disease. According to the leading theory about plague, a rat was a necessary vector to transport the fleas that carried the disease.



Animal plague in the U.S. by county, 1902–50
National Library of Medicine



Sylvatic plague cycle
CDC, AAI

In 1903, federal investigators found that workers on the Southern Pacific Railroad had contracted bubonic plague despite no evidence of contact with rats. Four years later, a fatal case of plague in Contra Costa County provided new clues as the investigation focused on local ground squirrels, which were found to be widely infected. Almost immediately upon arriving in California in 1913, Meyer had his first opportunity to see for himself how the U.S. Public Health Service (PHS) handled plague research under George McCoy (AAI 1916, president 1922–23).²⁷ Meyer learned how to identify plague via dissection of ground squirrels and was struck by how many infected animals the federal researchers discovered, confirming once and for all, that wild rodents were carriers of plague. But two years later, the PHS did something that Meyer considered “most unfortunate”—it announced that the fumigation of ground squirrel burrows had eradicated plague from California.²⁸ Of course, these measures had not actually solved the problem, and Meyer was asked to consult on a pneumonic plague outbreak in 1919.

Meyer was never one to allow himself to be confined to the lab; he was just as likely to be in the field hunting squirrels for dissection. A major breakthrough came in 1924, when squirrel fleas were found on rats in the middle of an outbreak in Los Angeles. Meyer began to believe that “under certain conditions squirrel plague could have been transmitted to rats and in rats it began to burn in a typical rat epizootic.”²⁹ After a similar outbreak in 1928, Meyer coined the term “sylvatic plague.” Unlike bubonic or pneumonic plague, sylvatic plague refers not to the type of *Yersinia pestis* infection, but rather to the reservoir of the bacterium situated in the wild rodent populations.³⁰ Under Meyer’s theory, plague outbreaks were not dependent on foreign vectors entering a port—the disease had made itself at home in the United States.

Human cases of plague kept appearing in places where no evidence of the disease had been found in the local fauna; to Meyer, this simply meant that existing methods of detection were inadequate. Taking a cue from the old

practices of the famed Japanese bacteriologist Kitasato Shibasaburo, who is credited with co-discovering the infectious agent of bubonic plague with Alexandre Yersin in 1894, Meyer began combing fleas from wild rodents and inoculating the fleas. This technique revealed that although there were no gross lesions in any of the thousand rodent specimens, samples from five percent of the fleas produced fatal plague in guinea pigs.³¹ From this data, Meyer hypothesized that the persistence of plague in a given area was dependent on how resistant the local rodent populations were. This new way of thinking about disease would soon dramatically alter public health strategies in California and the wider American West.

By 1935, the PHS and the California Department of Public Health were working with the Hooper Foundation to find and study plague throughout the Western states. They soon identified reservoirs in at least 12 states, in populations of ground squirrels, wood rats, chipmunks, prairie dogs, and marmots.³² Eventually, hundreds of wild rodent species were discovered to be carriers of plague. These discoveries led to the first wide-ranging rodent abatement programs on military bases, beginning close to San Francisco at Fort Ord.

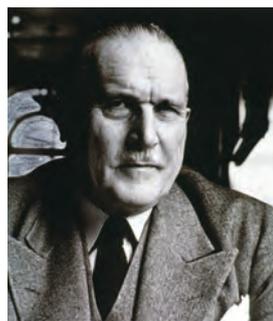
To study the transmission of *Yersinia pestis* more closely, Meyer sought to construct an entire “town” for his ever-increasing plague research. UCSF told him that it was too dangerous to “work with the black death” on campus, but the Rosenberg Foundation donated funds for a special secure laboratory where the work could be done safely.³³ One room held what became known as “Mouse Town, U.S.A.”—a large mouse enclosure split down the middle to allow tests of transmission and prophylaxis. The floor of the room was sprinkled with crystals of DDT and kept spotlessly white so any flea that managed to hop the walls of Mouse Town would be immediately visible.³⁴

Meyer placed 100 mice on each side of “town” and dosed the water of the west side with sulfadiazine. He then allowed 800 plague-infected fleas to invade Mouse Town with the freedom to cross the central barrier. Within days,



Karl F. Meyer in the laboratory
University of California, San Francisco, University Archives

plague was raging on the east side, but the sulfa-dosed mice on the west side remained healthy. Meyer's findings in this and other Mouse Town experiments led to antibiotic prophylaxis methods to prevent plague infection, as well as improved vaccines for plague. The isolation unit produced millions of doses of effective plague vaccine for military use: in 1964, not a single case of plague was reported throughout the U.S. armed forces, even among troops stationed in areas where plague infection occurred in the local population.³⁵



Karl F. Meyer
National Library of Medicine

Karl F. Meyer's tireless research was so foundational and wide-ranging that he won the 1951 Albert Lasker Basic Medical Research Award. This honor was not for any single discovery, but rather, for "Mechanism of parasites infection"—a fitting summary of decades of work. The Lasker committee recognized that Meyer bore:

*... a major share of responsibility for the control of botulism, and for a classification and international identification center for the clostridia; for our recognition that plague is sylvatic, not merely rat-borne; for understanding of the broad spectrum of brucellosis rather than restricted goat-borne Malta-fever; for the concept of ornithosis rather than psittacosis; for elucidating the role of the arthropod vector in western equine encephalomyelitis; for showing that western ticks are also responsible for relapsing fever; for studying the dinoflagellate causing mussel poisoning; for increasing our knowledge of leptospirosis; for valuable assistance with investigations of Q fever.*³⁶

In addition to his research, Meyer offered his professional service to government advisory committees, the National Academy of Science, the World Health Organization, and many professional organizations, including AAI. He served as the 27th president of AAI and, for over two decades, as an editor for *The Journal of Immunology*. He was also a dedicated, creative, and memorable educator who left his mark on generations of doctoral students. Meyer was a true renaissance immunologist whose wide-ranging work was invaluable to the field.

For more information on Karl F. Meyer, visit:
www.aai.org/About/History

¹ Karl F. Meyer, interview by Edna Tartaul Daniel, Regional Oral History Center, The Bancroft Library, University of California, Berkeley, 1961 and 1962, transcript, 27.

² Karl F. Meyer interview, 29.

³ Karl F. Meyer interview, 31.

⁴ Karl F. Meyer interview, 35–36.

⁵ Karl F. Meyer interview, 49–50.

⁶ Thelma Gutsche, *There Was a Man: The Life and Times of Sir Arnold Theiler K.C.M.G of Onderstepoort* (Cape Town: Howard Timmins, 1979), 262.

⁷ Karl F. Meyer interview, 62–63.

⁸ Karl F. Meyer interview, 68.

⁹ Karl F. Meyer interview, 72–73.

¹⁰ Karl F. Meyer, "The Animal Kingdom, a Reservoir of Human Disease," *Annals of Internal Medicine* 29, no. 2 (1948): 327.

¹¹ Ibid.

¹² Wilbur A. Sawyer, "Ninety-Three Persons Infected By a Typhoid Carrier at a Public Dinner," *Journal of the American Medical Association* LXIII, no. 18 (1914): 1537. Nine of the cases were considered "doubtful" but still worth including in the total; they showed signs "suggestive of mild typhoid fever" but were negative to the Widal test.

¹³ Karl F. Meyer interview, 85.

¹⁴ Karl F. Meyer interview, 256.

¹⁵ Karl F. Meyer interview, 253.

¹⁶ Karl F. Meyer interview, 255.

¹⁷ Karl F. Meyer interview, 212.

¹⁸ Meyer, "Animal Kingdom," 335.

¹⁹ Karl F. Meyer interview, 88–89. At the time, the organism was known as *Bacillus abortus*. In 1918, Meyer proposed the genus *Brucella* to honor David Bruce who had first connected the organism to "Malta Fever" in 1887.

²⁰ Karl F. Meyer interview, 89.

²¹ Karl F. Meyer interview, 95.

²² Karl F. Meyer interview, 96.

²³ About \$440,000 today.

²⁴ Karl F. Meyer interview, 99.

²⁵ Karl F. Meyer interview, 100.

²⁶ Dan C. Cavanaugh, "K. F. Meyer's Work on Plague," *The Journal of Infectious Diseases* 129 (1974): S10.

²⁷ Karl F. Meyer interview, 176–77.

²⁸ Karl F. Meyer interview, 177.

²⁹ Karl F. Meyer interview, 178–79.

³⁰ Karl F. Meyer interview, 180.

³¹ Karl F. Meyer interview, 180.

³² Karl F. Meyer interview, 181.

³³ Karl F. Meyer interview, 187; Marion Lewis Meyer, "A Brief History of the George Williams Hooper Foundation for Medical Research, University of California, San Francisco." J. Michael Bishop papers, MSS 2007-21, carton 19, folder 67, UC San Francisco Library, Special Collections, 7.

³⁴ James G. Chesnutt, "The AAAS-George Westinghouse Science Writing Awards for 1946: The Prize Winner," *The Scientific Monthly* 64, no. 1 (Jan. 1947): 77.

³⁵ Karl F. Meyer and Oliver R. McCoy, "Plague," in *Preventative Medicine in World War II, vol. VII: Communicable Diseases; Arthropodborne Diseases Other Than Malaria*, ed. John Boyd Coates (Washington, DC: Government Printing Office, 1964), 79.

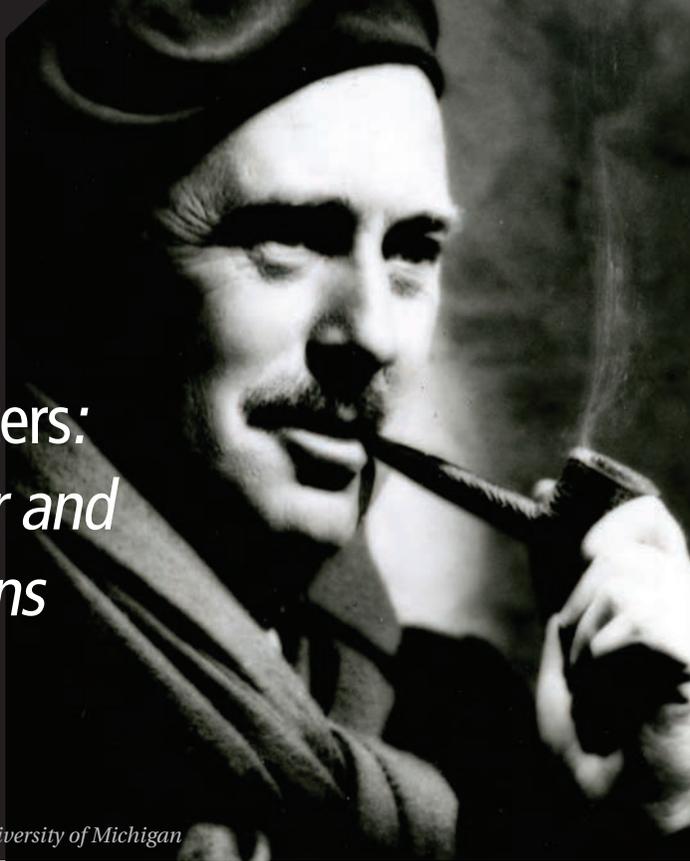
³⁶ Lasker committee quote from Albert D. Sabin, "Karl Friedrich Meyer, 1884–1974," in *Biographical Memoirs* (Washington, DC: National Academy of Sciences, 1980), 270.

HISTORY:
AAI LOOKS BACK

Paul de Kruif and Microbe Hunters: Revisiting an Early AAI Member and a Book That Inspired Generations

Paul de Kruif, c. 1932

University of Michigan Alumni Association records, Bentley Historical Library, University of Michigan



If one book, more than any other, drew scientists toward the field of immunology in the first half of the 20th century, it is most likely *Microbe Hunters* by Paul de Kruif (rhymes with “life”). The sweeping work of history—spanning Anton van Leeuwenhoek’s discovery of microbes in the 17th century through Paul Ehrlich’s “magic bullet” targeting syphilis in 1909—has remained in print since its original publication in 1926 and inspired not only generations of immunologists but also many adaptations as well.



Frederick G. Novy

AAI Collection, Center for
Biological Sciences Archive,
UMBC

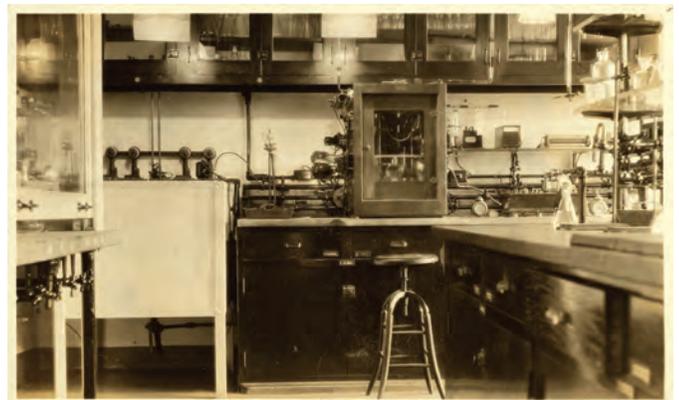
Legitimate scientific credentials were behind the fame de Kruif (AAI 1921) achieved as a writer of popular science. Having obtained his Ph.D. (1916) from the University of Michigan under the mentorship of Frederick Novy (AAI 1920, president 1924–25),¹ de Kruif enlisted in the U.S. Army and participated in the Mexican Expedition against Pancho Villa in 1916–17. Later, as a member of the Army’s Sanitary Corps

during World War I, he created a method for more rapid production of an antitoxin to *Clostridium perfringens*,² a major cause of gas gangrene during the war.³

Following the war and his return to the University of Michigan as an assistant professor, de Kruif fell in love with a laboratory assistant, Elizabeth (“Rhea”) Barbarin. Already married with two small children, de Kruif divorced his first wife and soon married Barbarin, which created a financial strain. To meet his new obligations,

de Kruif, at the encouragement of his literary idol, H. L. Mencken, undertook freelance writing while continuing his teaching and laboratory research with Novy.⁴ The latter endeavor soon proved fruitful, as his research on hemolytic streptococcus and anaphylatoxins caught the eye of scientists, including Simon Flexner (AAI 1920), at the Rockefeller Institute for Medical Research (RIMR; now the Rockefeller University).⁵

As a result of his growing prominence, de Kruif was appointed as an associate at RIMR and began work in the laboratory of Flexner. By then, however, de Kruif was already becoming disillusioned by the state of medical research and practice.⁶ He believed that increasing specialization was robbing the field of thoughtful generalists thus detaching it from the immediate needs of patients and allowing moral crusades to exert too much control over the direction of research.



Laboratory on the campus of the Rockefeller Institute for Medical Research, c. 1925

Courtesy of Science History Institute

de Kruif's first forays into writing about science, although published anonymously, nevertheless got him "fired" from Flexner's lab.⁷ In a series of four articles in *The Century Magazine* and a chapter in Harold E. Stearns's *Civilization in the United States*, de Kruif framed the medical field as becoming increasingly driven by profit, novelty, and moral crusading. He condemned this trend as "medical *Ga-Gaism*."⁸ When Flexner discovered the true authorship of the publications, he saw them as an attack on RIMR and asked for de Kruif's resignation in 1922.⁹ de Kruif complied but nonetheless published a collected and expanded edition of the offending essays dedicated to "my teacher of bacteriology... without his permission."¹⁰

de Kruif's dismissal from RIMR left him free to collaborate with celebrated author Sinclair Lewis on the Pulitzer-winning novel *Arrowsmith*, the story of a scientist torn between the rigors of pure science and the demands of public health crises. To prepare for the



Sinclair Lewis, c. 1925
Beinecke Rare Book and Manuscript Library, Yale University

novel, he and Lewis boarded a tramp steamer bound for the Caribbean. In the islands, they indulged in the sampling of tropical cocktails while producing a 60,000-word outline for the novel, drawing on their experiences in the region and de Kruif's scientific knowledge. Lewis was impressed, not only by de Kruif's technical contributions but also by his literary sensibilities. He later told H. G. Wells that de Kruif was "a man with a knife-edge mind and an iconoclasm that really means something."¹¹ The collaboration helped de Kruif as well: it taught him to write for a broader audience.

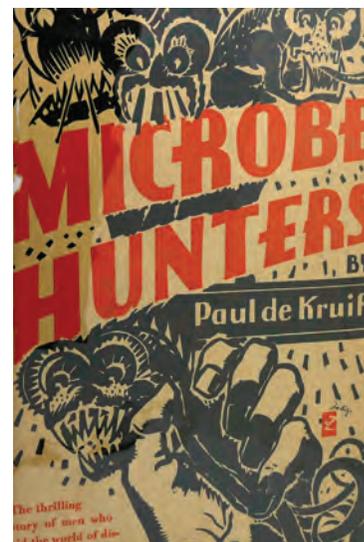
Arrowsmith was released in 1925 to wide critical acclaim. The book focuses on an issue that de Kruif had been weighing and writing about during the early part of the decade: the tension and conflict between medicine and basic research. The book's protagonist, Martin Arrowsmith, is a microbe hunter who, after finding success in the Midwest, is invited to join a highly respected biomedical research institute in New York—echoing the narrative of de Kruif's own life. It is in his capacity leading a biomedical research team that

Arrowsmith faces the life-changing dilemma of having to choose between being faithful to basic science and his principles or betraying them.

It was during his work with Lewis on *Arrowsmith* that de Kruif's next idea for a book emerged, with the sprouting of a seed planted years before by Jules Bordet, a colleague at RIMR. The work was to be a collection of stories profiling scientists and how their discoveries fundamentally altered the understanding of microbiology. de Kruif would start at the beginning with the microscope and carry his narrative to near-present day, covering this history by telling 12 stories of 14 scientists. To many in the public and the scientific community, *Microbe Hunters* was the nonfiction sequel to *Arrowsmith*.

In 1926, when *Microbe Hunters* was released, the field of immunology was still young and, at times, produced hypotheses and discoveries that were at odds with prevailing theories in some of the older, more established biomedical fields. In his presidential address that year, Wilfred H. Manwaring (AAI 1917, president 1925–26) acknowledged the "skepticism with which many of the theoretical phases of our subject have been received by works in the older medical sciences."¹² He attributed this skepticism, in large part, to disagreement over Ehrlich's receptor theory, which was being widely tested by new methods. Immunologists were also focused on the matter of blood typing, a topic of frequent discussion at the AAI annual meeting and in the pages of *The Journal of Immunology*.

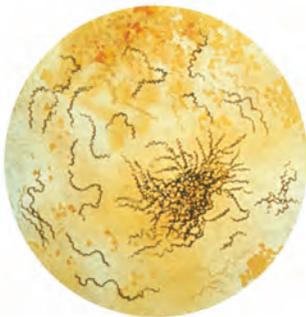
Microbe Hunters opens with a quartet of pioneers who established the existence of microscopic organisms and demonstrated their role in disease. The first of these is van Leeuwenhoek, who first saw miniscule animals through his revolutionary microscope in the 17th century. de Kruif's focus then turns to Lazzaro Spallanzani and the lengthy series of experiments he performed in an attempt to disprove spontaneous generation. Rounding out this section are Robert Koch's identification of specific pathogens and their connection to diseases, and Louis Pasteur's innovations in vaccines and the neutralization of microbes.



Microbe Hunters first edition cover, c. 1926

The book next focuses on the discoverers of mechanisms crucial to the immune system and understanding disease transmissions, as well as early developers of treatments and cures. By this time in the early 20th century, the hygiene theory was widely accepted, and the germ theory had been well established, thus making the modern biomedical setting more recognizable to the reader.

Elie Metchnikoff's discovery of macrophages ("the nice phagocytes") was a critical step in the understanding of innate immunity. Emile Roux and Emil von Behring developed the first successful diphtheria antitoxin, introducing serum therapy to the world. Theobald Smith (AAI 1920) proved that cattle were catching Texas fever from ticks, demonstrating that insects and other arthropods could act as disease vectors.



Treponema pallidum
Centers for Disease Control and Prevention

Smith's precedent led the way for the work of David Bruce (tsetse fly and sleeping sickness), Ronald Ross and Battista Grassi (mosquitoes and malaria), and Walter Reed (mosquitoes and yellow fever). The final microbe hunter featured in the book is Ehrlich, whose "magic bullet" against syphilis was the first example of successful chemotherapy treatment for a specific disease. de Kruif saw Ehrlich's achievement as the practical culmination of the centuries of research performed by the other scientists profiled in the book.

In most of his early science writing, de Kruif adopted a sensationalist tone—and in *Microbe Hunters*, he was practically breathless. In keeping with the heroic age of medicine, he made his subjects larger-than-life heroes, frequently imagining dialogue that they would exclaim at moments of discovery. A book review in *JAMA* noted that de Kruif described the innovators as "far from the perfect and rather priggish members of the human race that they are sometimes represented to be" but that his style had "an exaggerated quality which is annoying."¹³ The reviewer predicted that the book would be appreciated by scientists and a general audience alike.

Microbe Hunters found immediate and enormous success. It quickly became a national and international bestseller and was soon translated into 18 languages. Some subjects of the book, however, were less impressed. The most notable of these was Ross, the British scientist who received the 1902 Nobel Prize in Physiology or Medicine for identifying the role of the mosquito in malaria transmission.

Ross strenuously objected to how de Kruif portrayed his rivalry with Grassi. In an open letter, Ross, along with Aldo Castellani, George C. Low, David Nabarro, and Cuthbert Cristy, complained that de Kruif's account was "almost entirely apocryphal...not supported by reference to the original literature...[and] clearly derived almost only from his own imagination or from spurious prompting by others."¹⁴ Ross argued that some of de Kruif's statements went so far as to violate British libel laws—and indeed, the British edition of *Microbe Hunters* was published without the chapters on Bruce and Ross.¹⁵ Notwithstanding the controversy, the book was a bestseller and has remained a staple of medical history.

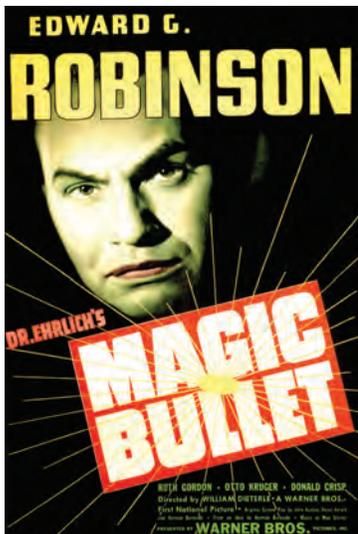
The impact of *Microbe Hunters* went far beyond the printed page. In the 1930s and '40s, adaptations of the book made their way to stage, radio, and screen, usually with de Kruif's involvement. The author collaborated with another Pulitzer winner, Sidney Howard, to transform his chapter on Walter Reed into the play *Yellow Jack* in 1934.

The story of Reed battling yellow fever in Cuba at the end of the Spanish–American War gave a young Jimmy Stewart his first dramatic stage role as a young private who volunteers to be bitten by a mosquito in hopes of proving the method of transmission. Critics praised *Yellow Jack*, but this early translation from book to stage was not a hit at the box office.¹⁶ Nevertheless, four years later, the play was successfully adapted for the screen; the film's cast featured Lewis Stone, who had actually served in the Spanish–American War, as Reed.

Under the Works Progress Administration of the New Deal, the Federal Theatre Project (FTP) produced hundreds of classic and original plays, including one adapted from de Kruif's chapter on Ehrlich, with the unlikely title *Spirochete*. The play premiered in Chicago in 1938, just two years after U.S. Surgeon General Thomas Parran famously declared war on syphilis. *Spirochete* was a huge success, especially considering that the word "syphilis" had been considered almost too obscene for print just one year before. Theatergoers could even take a Wasserman test in the lobby during intermission.¹⁷ The show's Seattle run was



Yellow Jack poster, c. 1938



Dr. Ehrlich's Magic Bullet poster, c. 1940

National Library of Medicine

dramatizing four of de Kruif's books of popular science for a national radio audience.

The best known adaptation of *Microbe Hunters* is the 1940 film *Dr. Ehrlich's Magic Bullet*, another production that pushed the boundaries of what was considered decent for the screen. Its topic was technically prohibited by the Motion Picture Production Code

the most successful FTP production in the city, with 3,000 people attending the performances.¹⁸

Americans did not have to go to the theater to hear stories of microbe hunters; they could also tune in to a weekly radio series. The FTP worked with de Kruif to adapt *Microbe Hunters* as the first 14 episodes of the radio drama series *Men Against Death*. The series ran weekly from June 30, 1938, to April 22, 1939, on the CBS network,

of 1934, which stated that “sex hygiene and venereal diseases are not acceptable subject matter for theatrical motion pictures.”¹⁹ Nevertheless, the search for a chemotherapeutic cure for syphilis was dramatized in a high-profile movie starring Edward G. Robinson as Ehrlich, with an Oscar-nominated script by John Huston.

The bulk of the film was shot in black and white, but the views of microscope slides were in Technicolor. In lieu of actual microphotography, however, the filmmakers used rubber models of syphilis spirochetes on giant slides and injected dye into them while activating them from below with wires.²⁰ Critics praised the film for both its bold approach to a difficult topic and the performances of the cast.

For decades after its publication, *Microbe Hunters* was an inspiration and springboard for future biomedical researchers and doctors, and the book launched a new genre of science writing that flourishes to this day. Outdated as it is by current measure, both in terms of historical rigor and antiquated racial overtones, *Microbe Hunters* remains a classic documentary of the earliest microbiologists and immunologists and serves as an inspiration to new scientists. Today, de Kruif's fast-paced narrative continues to be relevant to a wide audience as an exciting entry point into the origins of immunology and the field-shifting discoveries of its early years.

¹ An abbreviated version of de Kruif's dissertation was published in 1917. Frederick G. Novy and Paul H. de Kruif, “Anaphylatoxin and Anaphylaxis,” *Journal of the American Medical Association* 68, no. 21 (1917): 1524–8. In addition, 10 articles of the 11-part “Anaphylatoxin and Anaphylaxis” series appeared in *The Journal of Infectious Diseases* beginning in May and June 1917. The final article was published in the same journal in the June 1919 issue.

² This species of bacterium was previously referred to in scientific literature as *Clostridium welchii* and *Bacillus welchii*. de Kruif was familiar with *C. perfringens* before his deployment during the war. See Paul H. DeKruif, Theodore W. Adams, and Paul M. Ireland, “The Toxin of Bacillus Welchii: I Toxin Production by Various Strains,” and Paul H. DeKruif and Jesse L. Bollman, “The Toxin of Bacillus Welchii: II The Mechanism of Infection with B. Welchii,” *The Journal of Infectious Diseases* 21, no. 6 (1917): 580–601.

³ Albin Krebs, “Dr. Paul de Kruif, Populizer of Medical Exploits, Is Dead,” *New York Times*, March 2, 1971.

⁴ Krebs, “Dr. Paul de Kruif,” *New York Times*.

⁵ Paul H. de Kruif and Paul M. Ireland, “Streptolysin,” *The Journal of Infectious Diseases* 26, no. 4 (1920): 285–329. For de Kruif's publications on anaphylatoxins, see endnote 1.

⁶ Eli Chernin, “Paul de Kruif's *Microbe Hunters* and an Outraged Ronald Ross,” *Reviews of Infectious Diseases* 10, no. 13 (1988): 661.

⁷ While it is unclear whether de Kruif was asked to resign or was fired, de Kruif claimed multiple times that he was fired. Krebs, “Dr. Paul de Kruif,” *New York Times*.

⁸ Paul de Kruif, “Medicine,” in *Civilization in the United States: An Inquiry by Thirty Americans*, ed. Harold E. Stearns (New York: Harcourt, Brace and Co., 1922), 449.

⁹ H. M. Fangerau, “The Novel *Arrowsmith*, Paul de Kruif (1890–1971) and Jacques Loeb (1859–1924): A Literary Portrait of ‘Medical

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¹⁰ Paul de Kruif, *Our Medicine Men* (New York: The Century Co., 1922), v.

¹¹ Sinclair Lewis, quoted in James M. Hutchisson, “Sinclair Lewis, Paul de Kruif, and the Composition of *Arrowsmith*,” *Studies in the Novel* 24, no. 1 (1992): 52.

¹² Wilfred H. Manwaring, “The Basic Concepts of Immunity,” *The Journal of Immunology* 60, no. 3 (1926), 177.

¹³ “Book Notices,” *Journal of the American Medical Association* 86, no. 17 (1926): 1310.

¹⁴ Aldo Castellani, George C. Low, David Nabarro, and Ronald Ross, “‘Microbe Hunters’—A Denial,” *Journal of the American Medical Association* 87, no. 16 (1926): 1321. Castellani, Nabarro, and Cristy appeared in de Kruif's chapter on David Bruce.

¹⁵ Eli Chernin, “Paul de Kruif's *Microbe Hunters* and an Outraged Ronald Ross,” *Reviews of Infectious Diseases*, 10 no. 3 (1988): 665.

¹⁶ Hamilton Wright, “He Said It Was History,” *Brooklyn Daily Eagle*, July 8, 1934.

¹⁷ Allan M. Brandt, *No Magic Bullet: A Social History of Venereal Disease in the United States Since 1880* (New York: Oxford University Press, 1987), 152.

¹⁸ Sarah Guthu, “Living Newspapers: Spirochete,” in *The Great Depression in Washington State*, University of Washington, http://depts.washington.edu/depress/theater_arts_living_newspaper_spirochete.shtml (accessed October 19, 2018).

¹⁹ Quoted in Nancy Tomes, “Epidemic Entertainments: Disease and Popular Culture in Early-Twentieth-Century America,” *American Literary History* 14, no. 4 (2002): 646–47.

²⁰ Douglas W. Churchill, “News and Views from Hollywood,” *New York Times*, January 14, 1940.

From Benches to Trenches: AAI in the First World War

“**W**hen the history of the present great war is written a notable victory over the common enemy, disease, will be recorded as one of the greatest triumphs in this greatest of all conflicts.” Thus began John A. Kolmer’s AAI president’s address in the early spring of 1918. The three factors Kolmer believed would lead to a “triumph over disease” were “prevention by sanitary measures, specific immunization and improved methods of treatment of the inevitable and unavoidable sick and injured.”

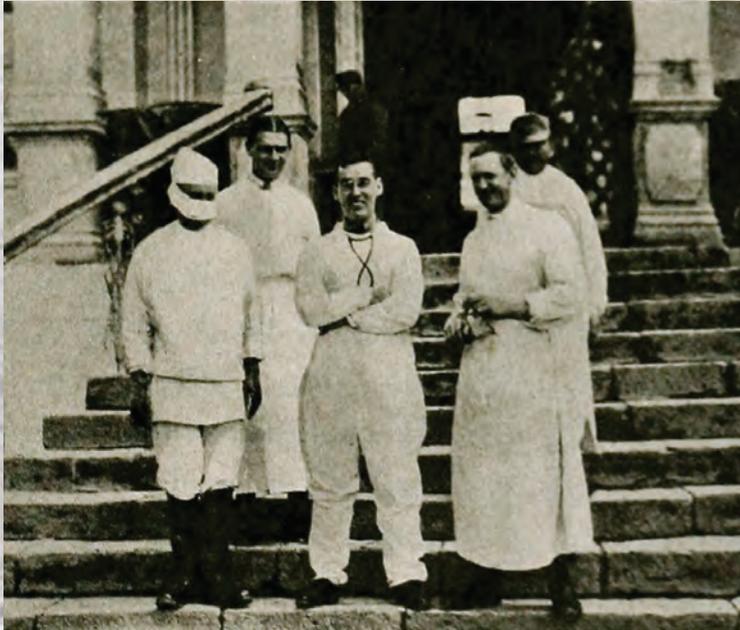
To this end, many members of AAI joined the war effort when the United States entered in 1917—the third year of the war—in many different roles. Some focused on wartime research in their own laboratories. Others joined the U.S. Army Sanitary Corps or Medical Department, which coordinated research in U.S. and European labs. A few, including future AAI president Stanhope Bayne-Jones, volunteered to fight in the trenches.

Here we commemorate the ending of the war with the Armistice on November 11, 1918, one hundred years ago.

Red Cross workers carry a wounded man over the top of a trench.
Photo courtesy Library of Congress



Including physicians, nurses, and support personnel, the U.S. Army Medical Department recruited 250,000 men and women by the end of the war, greatly limiting the effects of disease.
Photo courtesy Library of Congress



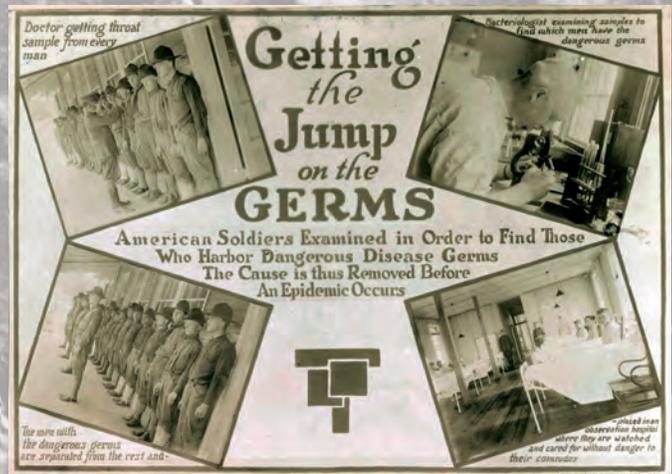
Hans Zinsser (AAI 1917, president 1919–1920, pictured center) went to Europe with the American Red Cross in 1915 to fight the typhus epidemic in Serbia. His experiences there helped inspire his 1935 book *Rats, Lice and History*. Photo from *Typhus Fever: With Particular Reference to the Serbian Epidemic*, by Richard P. Strong, et al, 1920.



Oswald T. Avery (AAI 1920, president 1929–30, pictured right) spent the war stateside in the U.S. Army Medical Corps, working on influenza research. He could not be made an officer because he was still a Canadian citizen, but his service helped him qualify for U.S. citizenship. Photo courtesy National Library of Medicine



Stanhope Bayne-Jones (AAI 1917, president 1930–31, pictured front row, center) volunteered to serve with the British Expeditionary Force and arrived at the front nearly a year before the bulk of the U.S. forces. He later transferred to the 26th Infantry Division of the U.S. Army, known as the Yankee Division. Photo courtesy National Library of Medicine



Apart from the influenza pandemic, advances in preventative medicine greatly reduced casualties from disease compared to previous wars.

Photo courtesy National Archives



Through a massive volunteer effort, the American Red Cross produced enormous numbers of masks to prevent the spread of influenza among both soldiers and civilians.

Photo courtesy National Archives



Lice that spread epidemic typhus were a serious concern on the front. This 8,000 pound steam sterilizer could kill those "cooties," as the soldiers called them, on the gear of forty men at a time.

Photo courtesy National Archives



In the close quarters of an Army influenza ward, patients were often isolated by sheets and arranged in an alternating head-to-foot pattern. The scale of the epidemic forced the issue of racial integration in many Army hospitals.

Photo courtesy National Library of Medicine



Incidence of sexually transmitted disease among army personnel was much lower than in the civilian population, thanks to intensive campaigns of education. Soldiers returning home were reminded to maintain the precautions they had learned in the military.

Photo courtesy Library of Congress

Immunology in San Diego: Staking Claims on Torrey Pines Mesa

Torrey Pines looking south, 2017
Chris Nelson, Flickr

Along the sandstone cliffs overlooking the Pacific Ocean in the north end of San Diego lies Torrey Pines Mesa, home to acres of preserved natural beauty and the unique conifer that gives the place its name. Since 1961, the mesa has also been the nexus of immunological research in the region. The history behind San Diego's community of universities, research institutes, and biotech companies, however, starts at the beginning of the twentieth century.

The Early Decades



Ellen Browning Scripps, 1919
Scripps Institution of Oceanography Photographs, UCSD

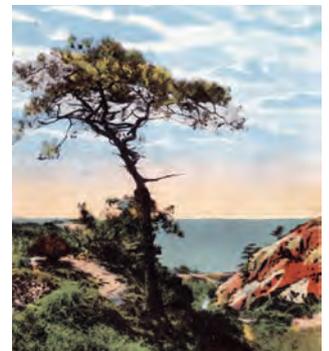
\$300,000 toward the founding of the Scripps Memorial Hospital and Scripps Metabolic Clinic to investigate and treat diseases, especially diabetes.²

During the Second World War, Torrey Pines had been the location of Camp Callan, a U.S. Army anti-aircraft training facility. Though postwar demobilization brought a significant reduction in the military presence in San Diego, a U.S. Marine Corps rifle range at Camp Matthews continued

Bioscience research in San Diego began in 1909 when newspaper magnate and philanthropist Ellen Browning Scripps donated \$150,000 to the University of California Regents to support the Marine Biological Laboratory in La Jolla, the western hemisphere's first permanent marine science center.¹ At the time, the city's population was a mere 39,500 people. In 1924, inspired by the discovery of insulin, Scripps contributed an additional

to occupy a sizable portion of the mesa. With San Diego's population rapidly expanding—it would reach 573,224 by the end of the 1950s—many residents of La Jolla, the increasingly affluent San Diego neighborhood just north of downtown, were growing more uncomfortable living so close to an active range.³

At the same time, three endeavors were underway that would help define the future of the mesa. The Scripps Clinic, which separated from the hospital and became the Scripps Clinic and Research Foundation, was actively recruiting biomedical scientists for its new research facility. Jonas Salk (AAI '47) had begun searching for a site where he could establish a research institute following his success with the polio vaccine. And the University of California set its sights on building a new campus in the area.



Postcard of a Torrey Pine, 1925
Baja California and the West Postcard Collection, UCSD



Recruits on the pistol range at Camp Matthews, 1950
National Archives

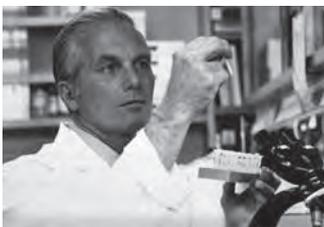
With more than enough available land for all three institutions on the Torrey Pines Mesa, the city of San Diego found itself in a unique and enviable position. The city owned the rights to 49,000 acres of pueblo lands on the mesa and surrounding areas, and business and civic leaders decided to use that land to attract scientific research to the area.

University of California, San Diego

The University of California was the first to take advantage of the newly available real estate. Roger Revelle, then the director of the Scripps Oceanographic Institute, led the push to create an entirely new campus in San Diego rather than expanding the Los Angeles campus. General Dynamics, a large defense and aerospace company, helped ensure that the city would provide the land for it by promising to invest \$1 million in the university.⁴ With this guarantee, the University of California, San Diego (UCSD), was officially established on November 18, 1960, as a school focused on “mathematics, physics, chemistry, and the earth and biological sciences.”⁵ As part of the initial campaign of recruitment, S. Jonathan Singer (AAI ’70) came to UCSD from Yale University in 1961 to join the new Department of Biology, where his research led to the fluid mosaic model of the cell membrane.⁶

Fewer than 25 years after admitting its first class of undergraduates, UCSD was one of the top recipients of NIH funding, ranking 16th out of 1,636 institutions in 1987, with \$73 million in grants.⁷

Scripps Research



Frank Dixon, 1970
National Library of Medicine

The establishment of UCSD on Torrey Pines Mesa opened up new possibilities for other institutions, and Scripps moved quickly to stake a claim of its own. The director, Edmund Keeney, wanted to transform the

small clinic into “a Rockefeller Institute of the West Coast.”⁸ To launch the new Division of Experimental Pathology in 1961, Scripps recruited Frank J. Dixon



UCSD Revelle College campus under construction, 1964
Charles H. Graves Photographs and Films, UCSD

(AAI ’50, president 1971–1972) and the rest of the “Pittsburgh Five,” a group of immunologists from the University of Pittsburgh. Dixon, William O. Weigle (AAI ’57), Charles G. Cochrane (AAI ’61), Joseph D. Feldman (AAI ’63, editor-in-chief, *The Journal of Immunology*, 1971–1987), and Jacinto “Joe” Vazquez (AAI ’59) brought several postdocs and other laboratory staff with them to La Jolla, forming the foundation of immunological research at Scripps.⁹

By 1970, Dixon was the chair of biomedical operations at Scripps and, in 1974, he was made director of the entire research institute. Under his leadership all operations were consolidated at the new Torrey Pines campus in 1980. Since the arrival of the Pittsburgh Five in La Jolla, Scripps has consistently employed the largest number of AAI members in the San Diego area.

Salk Institute

Seeking a suitable spot in California to found his new institute, Jonas Salk was initially leaning toward the San Francisco Bay area. On a scouting visit to Palo Alto, Salk got



Salk Institute for Biological Studies buildings, designed by Louis Kahn
Library of Congress

to know Melvin Cohn (AAI ’51; remembered on page 58 of this issue), then a recent arrival at Stanford, as they drove around looking at potential sites. When Revelle invited Salk to La Jolla, however, he was impressed not only with the beauty of Torrey Pines Mesa, but also the opportunity to join a nascent community of research institutions.¹⁰



Jonas Salk with Edward R. Murrow, 1966
National Library of Medicine

Unfortunately for Revelle, Salk successfully convinced the city of San Diego to grant him a prime strip of 27 acres overlooking the Pacific Ocean that Revelle had hoped would go to UCSD,

leading to a bitter public conflict.¹¹ Funding from the March of Dimes allowed construction of the Salk Institute for Biological Studies to begin in 1962.

In 1963, the first laboratory opened on the Salk Institute campus, boldly designed by famed architect Louis Kahn to promote collaborative work. Cohn was part of the inaugural cohort of six resident fellows hand selected by Salk and was also one of the organizers of the landmark 1965 Antibody Workshop in Warner Springs. At that gathering just outside of San Diego, immunologists and molecular biologists found common ground—and the modern direction of immunology took shape.¹²

Legacy

The founding of the “big three” institutions on Torrey Pines Mesa—Scripps, UCSD, and Salk—established a beachhead for bioscience research in San Diego. Others quickly followed. In 1976, what is now known as the Sanford Burnham Prebys Medical Discovery Institute was founded as the La Jolla Cancer Research Foundation. More recently, the La Jolla Institute for Immunology, founded in 1989 by Kimishige Ishizaka (AAI '58, president 1984–1985) and Teruko Ishizaka (AAI '65), has grown rapidly to become the professional home to one of the region's largest contingents of AAI member researchers.

Over the past 40 years, San Diego has also become a major hub for the biotech industry. In 1978, UCSD professor Ivor Royston launched the region's



Hybritech, the first biotech company in San Diego

Courtesy of Science History Institute

first biotech company, Hybritech, which was a pioneer in the use of monoclonal antibodies. The company's alumni have gone on to found dozens of other firms in San Diego.¹³ AAI members have founded or conducted research at more than 100 biotech companies in the area, which today include BioLegend, BD Pharmingen, Thermo Fisher Scientific, AnaptysBio, Arena Pharmaceuticals, and NantKwest.

In 1989, Ralph Reisfeld (AAI '67) noted one obvious measure of the success of immunology and biomedical research in San Diego. Scientists, as he put it, no longer had to ask how to spell “La Jolla.”¹⁴

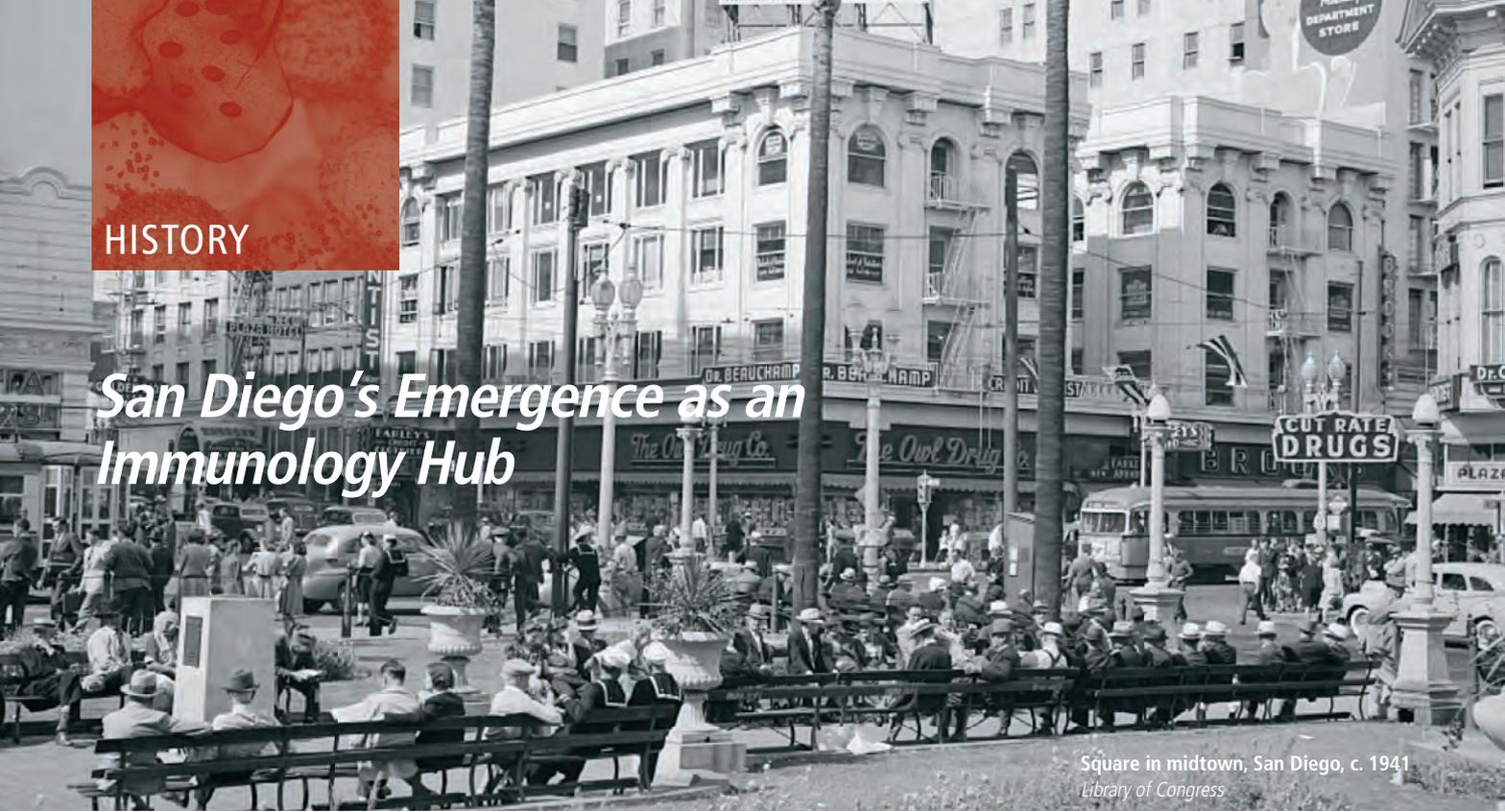
**More information about the history of immunology in San Diego
will be featured in a special exhibit at IMMUNOLOGY 2019™.**

References

1. Ellen Browning Scripps (1836–1932) with her brother E.W. Scripps founded the largest newspaper chain in the United States in the early 20th century. She became one of the largest philanthropists in Southern California with her fortune that was over \$3 billion in today's money. In addition to the Marine Biological Laboratory and Scripps Memorial Hospital and Scripps Metabolic Clinic, she helped establish or fund Scripps College and the Torrey Pines State Reserve, among others.
2. Mary Lindenstien Walshok and Abraham J. Shragge, *Invention and Reinvention: The Evolution of San Diego's Innovation Economy* (Redwood City, CA: Stanford University Press, 2014), 91.
3. Walshok and Shragge, *Invention and Reinvention*, 93.
4. Walshok and Shragge, *Invention and Reinvention*, 80.
5. Walshok and Shragge, *Invention and Reinvention*, 81.
6. S. J. Singer and Garth L. Nicolson, “The Fluid Mosaic Model of the Structure of Cell Membranes,” *Science* 175, no. 4023 (1972): 720–31.
7. Kathryn Phillips, “Closing in on Cancer,” *Los Angeles Times Magazine*, February 19, 1989, 12.
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10. Bourgeois, *Genesis of the Salk Institute*, 61–63.
11. Bourgeois, *Genesis of the Salk Institute*, 69.
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HISTORY

San Diego's Emergence as an Immunology Hub

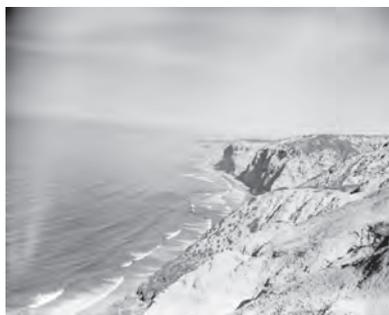


Square in midtown, San Diego, c. 1941
Library of Congress

The history exhibit at IMMUNOLOGY 2019™ showcased the rich history of immunology in San Diego. Although the city is a relatively new center for the field, it has long roots in biological research and has rapidly become an important hub of innovation. In the March/April 2019 issue of the *AAI Newsletter*, we looked at the pioneers of immunology on Torrey Pines Mesa. Here, drawing on the IMMUNOLOGY 2019™ history exhibit, we explore additional aspects of immunological history in San Diego.

The Growth of Immunology in San Diego

The first members of The American Association of Immunologists (AAI) in San Diego, beginning in 1961, were scientists at the Scripps Research Institute. For most of the 1960s, the only two institutions in San Diego with AAI members were Scripps and the Salk Institute. In the middle of the decade, the University of California, San Diego (UCSD), began an intense recruitment campaign to attract



Torrey Pines Bluff, La Jolla, c. 1948
Milo Woodbridge Williams Photographs, UCSD

top scientists, including immunologists, to the institution. By the late 1970s, immunology was flourishing at all of the “Big Three” institutions on Torrey Pines Mesa, with the local AAI membership growing from zero to nearly 100 in less than two decades.



Map of biotech companies with AAI members in San Diego
AAI

The local biotechnology industry was born in 1978 with the founding of Hybritech and quickly became represented in the AAI membership. Hybritech, founded by UCSD professor Ivor Royston (AAI '81), was a pioneer in the use of monoclonal antibodies, and its alums have gone on to found dozens of other firms in San Diego, such as Dura, IDEC, and Viagene. By 1990, AAI was represented at over a dozen companies in San Diego. That number doubled by the turn of the century. AAI members have founded or conducted research at more than 100 biotech companies in the area, which today include BioLegend, BD PharMingen, Thermo Fisher Scientific, AnapTysBio, Arena Pharmaceuticals, and NantKwest.

The last two decades have been marked by diversification in research opportunities, as new biotech firms and research institutes were founded, and joint centers and partnerships between institutions on the mesa were established. AAI members are now well represented at a variety of research environments in San Diego, with the largest numbers at UCSD, Scripps Research, and the La Jolla Institute for Immunology.

Distinguished Members

Once Frank Dixon (AAI '50, president 1971–72) and the rest of the “Pittsburgh Five” arrived at Scripps Research in 1961, and Jonas Salk (AAI '47) established the Salk Institute, San Diego began to attract many distinguished AAI members.

The first AAI president to serve his term in San Diego was Karl Habel (AAI '52, president 1969–70) who, following a long tenure at the National Institutes of Health (NIH), was recruited in 1967 to continue his research and teaching at Scripps and UCSD. Richard Dutton (AAI '63, president 1995–96) came to La Jolla from London in 1962, initially to



Richard W. Dutton, 1972
Scripps Institution of
Oceanography Photographs,
UCSD

perform research at Scripps before moving his laboratory to UCSD in 1968, where he spent almost three decades conducting research using in vitro studies of the antibody response and T cell response. Jonathan Sprent (AAI '80, president 1998–99) arrived at Scripps in 1984, where for nearly two decades he conducted research elucidating the role of the T cell. The most recent president from San Diego is Linda Sherman (AAI '81, president

2014–15) who, since joining Scripps in 1978, has made discoveries connected to the interface between autoimmunity and tumor immunity.

In addition to these past presidents, San Diego has also been home to Joseph Feldman (AAI '63, EIC 1971–87), the second longest serving editor-in-chief of *The Journal of Immunology*; Mitchell Kronenberg (AAI '84, secretary-treasurer 2009–15), who since 2003 has been president and chief science officer at the La Jolla Institute for Immunology (LJI); recipients of the AAI Excellence in Mentoring Award Norman R. Klinman (AAI '67) in 2006 and Michael B.A. Oldstone (AAI '70) in 2011; and members of the inaugural class of the Distinguished Fellows of AAI Wendy L. Havran (AAI '85), Stephen M. Hedrick (AAI '81), Kronenberg, and Sherman.



Linda A. Sherman, c. 2014
AAI

Institutions

The expansion of immunology in San Diego included the establishment of independent non-profit research institutes beginning in the 1970s. Three of the earliest that brought many AAI members to San Diego were the La Jolla Cancer Research Institute (now the Sanford Burnham Prebys Medical Discovery Institute), the Medical Biology Institute, and the La Jolla Institute for Allergy and Immunology (now the La Jolla Institute for Immunology).

Sanford Burnham Prebys Medical Discovery Institute was established when William and Lillian Fishman left Tufts University, set off for San Diego in 1976 with

a \$180,000 planning grant from the National Cancer Institute, and founded the La Jolla Cancer Research Foundation.¹ The early pioneers on Torrey Pines Mesa made the Fishmans feel at home: the Scripps Research Institute provided laboratory space for the fledgling foundation, and Jonas Salk visited to offer an electron microscope.² In 1979, Erkki Ruoslahti (AAI '77) joined the foundation and, under his leadership, it grew rapidly and produced many innovations in cancer immunology, particularly in the area of extracellular matrix proteins.³ John C. Reed (AAI '97) made important discoveries of the proteins involved in apoptosis and their mechanism in



The Pitt News front page, March 21, 1960
The Pitt News

Ellen Browning Scripps and the Birth of Scripps Research

Biological science in San Diego owes a great debt to one woman. Ellen Browning Scripps was the embodiment of the American Dream and the new dynamism of women in the early 20th century. An immigrant, journalist, entrepreneur, and philanthropist, she became one of the most important leaders in the creation and development of San Diego scientific and educational institutions.

Scripps was born October 18, 1836, in London, England. When she was seven, she emigrated with her family to Rushville, Illinois. Scripps matriculated at Knox College, one of the few institutions of higher learning to admit women, where she studied science and mathematics and earned her certificate in 1859 (no diplomas were awarded to women at that time). While at Knox she witnessed, on October 7, 1858, one of the Abraham Lincoln-Stephen A. Douglas debates. She later returned to Rushville and became a teacher.

After the Civil War, Scripps moved to Detroit to work in the family business, *The Detroit Evening News*, the newspaper that launched the Scripps publishing empire. There, she acted as a proofreader and writer of front-page features that included columns on women's suffrage and prohibition. She built a fortune by investing her own money in, and advising, the Scripps Publishing Company run by her brother, E. W. Scripps. The company soon grew to become the largest newspaper chain in the United States, with major papers first in the Midwest and then Western cities.



Downtown San Diego, c.1915
Library of Congress

of the new century, Scripps had become a pillar of the local community, engaged personally and philanthropically in a growing number of progressive causes.



Ellen Browning Scripps, 1919
Scripps Institution of Oceanography Photographs, UCSD

In the early 1890s, Ellen and E.W. bought land in San Diego (Miramar Ranch), where they lived until 1897 when she built a seaside cottage in La Jolla. By the first decade

Scripps' philanthropic interests were focused almost exclusively on educational and scientific endeavors. In San Diego, she helped establish or fund the Bishop's School; La Jolla Woman's Club; Children's Pool; Torrey Pines State Reserve; Scripps Aquarium (now Birch Aquarium at Scripps); San Diego Zoo; and many museums, libraries, and arts programs. Outside of San Diego, she founded Scripps College in Claremont, California, and was benefactor of educational and scientific programs as far away as Cleveland, Ohio. Additionally, Scripps helped establish two world-renowned scientific institutions located in San Diego—Scripps Institution of Oceanography and Scripps Research.

Scripps Institution of Oceanography

Initially established in June 1903 as the Marine Biological Association (MBA) of San Diego, the independent research laboratory was funded by Ellen and E. W. for its first decade, which included a move to its current location in La Jolla and construction of its first permanent laboratory. Individually, Ellen bequeathed \$150,000 in 1909 to support a permanent location in La Jolla, and from 1913 to 1916 donated \$130,000 for the construction of additional campus facilities, including the iconic pier.¹ In 1912, after the MBA deeded its property to the University of California Board of Regents, the facility was renamed Scripps Institution for Biological Research; the current name was conferred in October 1925.

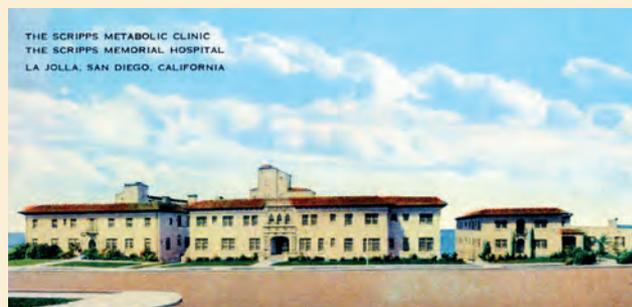


Scripps Institution of Oceanography
Scripps Institution of Oceanography Photographs, UCSD

Scripps Research

In 1924, inspired in part by the revolutionary discovery of insulin by Frederick Banting and Charles Best in the early 1920s, Scripps founded the Scripps Memorial Hospital (now Scripps Health) and, within it, the Scripps Metabolic Clinic, a research facility with the mission to investigate and treat diseases, especially diabetes. When Scripps died in 1932, she left the clinic \$300,000 (~\$5.5 million today) “preferably for research.”² In 1946, the clinic separated from the hospital and began to build new research facilities and recruit scientists. Today it is known as Scripps Research.

On February 22, 1926, Scripps became one of the first women to appear on the cover of *Time* magazine, which recognized her for her many philanthropic efforts and called her the “most beloved woman in Southern



Scripps Metabolic Clinic

Baja California and the West Postcard Collection, UCSD

California.” It is estimated that her lifetime donations amounted to over \$36 million in 2018 dollars. Scripps died at her home in La Jolla on August 3, 1932, a few weeks before her 96th birthday.

¹ Elizabeth Shor, Deborah Day, Kevin Hardy, and Dora Dalton, “Scripps Timeline,” *Oceanography* 16, no. 3 (2003), 111–12.

² Mary Lindenstein Walshok and Abraham J. Shragge. *Invention and Reinvention: The Evolution of San Diego's Innovation Economy* (Redwood City, CA: Stanford University Press, 2014), 91.

anti-cancer drugs. The advances made by researchers at the foundation attracted the attention of generous donors, prompting several name changes over the years; it has been known as Sanford Burnham Prebys Medical Discovery Institute since 2015.

The Medical Biology Institute (MBI) was founded in 1982 on the Torrey Pines Mesa by David Katz (AAI '72), a former Scripps researcher, and within a few years had provided the field with an invaluable tool. In 1988, a research group at MBI led by Donald Mosier (AAI '69) was one of the first to create a functioning immune system in a mouse.⁴ Using the severe combined immunodeficiency mouse that Melvin Bosma (AAI '96) had developed in 1983, Mosier's team injected human peripheral blood leukocytes into the peritoneal tissue of the mouse's chest, creating mice that could produce human antibodies.⁵

The La Jolla Institute for Immunology (LJI) has quickly grown to become one of the top three employers of AAI members in San Diego. Founded in 1988 as the La Jolla Institute for Allergy and Immunology by a group of scientists from academia and industry, LJI began

laboratory operations the next year with the arrival of Kimishige Ishizaka (AAI '58, president 1984–85) and Teruko Ishizaka (AAI '65) from Johns Hopkins University. Kimishige Ishizaka was appointed president and scientific director of the institute in 1991. In subsequent years, LJI has been led by AAI members Howard Grey (AAI '65) and Kronenberg. From the very beginning, LJI has maintained the world's longest running industry-academic partnership in its collaboration with the Japanese pharmaceutical firm Kyowa Kirin Pharmaceutical Research. The firm has first negotiating rights to translate basic research discoveries stemming from those Institute projects that it funds.⁶ In La Jolla, the Institute and company share adjoining laboratory facilities on the edge of the UCSD campus.

The growth and diversification of immunology research in San Diego has probably far exceeded the dreams of Frank Dixon and the Pittsburgh Five when they arrived to set up the first immunology laboratories in San Diego. Nearly six decades later, the city is a thriving hub of immunology investigation and discovery at its many research centers and biotech companies.

¹ “Building a Foundation: Q&A with Lillian Fishman,” *San Diego Union-Tribune*, April 27, 2013.

² “Building a Foundation.”

³ Kathryn Philips, “Closing in on Cancer,” *Los Angeles Times Magazine*, February 19, 1989, 16.

⁴ The other team that made a similar innovation at the same time was led by Irving L. Weissman (AAI '71, president 1994–95) at the Stanford University School of Medicine.

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⁶ “La Jolla Institute Renews Longtime Collaboration with Kyowa Kirin Pharmaceutical Research, Inc.,” La Jolla Institute, December 18, 2018. www.lji.org/news-events/news/post/la-jolla-institute-renews-longtime-collaboration-with-kyowa-kirin-pharmaceutical-research-inc

A Brief Timeline of Immunology in San Diego

- 1924** Ellen Browning Scripps founds Scripps Metabolic Clinic (renamed Scripps Clinic and Research Foundation in 1956)
- 1960** University of California, San Diego (UCSD) established and Salk Institute for Biological Studies founded
- 1961** "Pittsburgh Five," Frank Dixon (AAI '50), William Weigle (AAI '57), Joseph Feldman (AAI '63), Charles Cochrane (AAI '61), and Jacinto Vazquez (AAI '59), move from University of Pittsburgh to establish Division of Experimental Pathology at Scripps Research

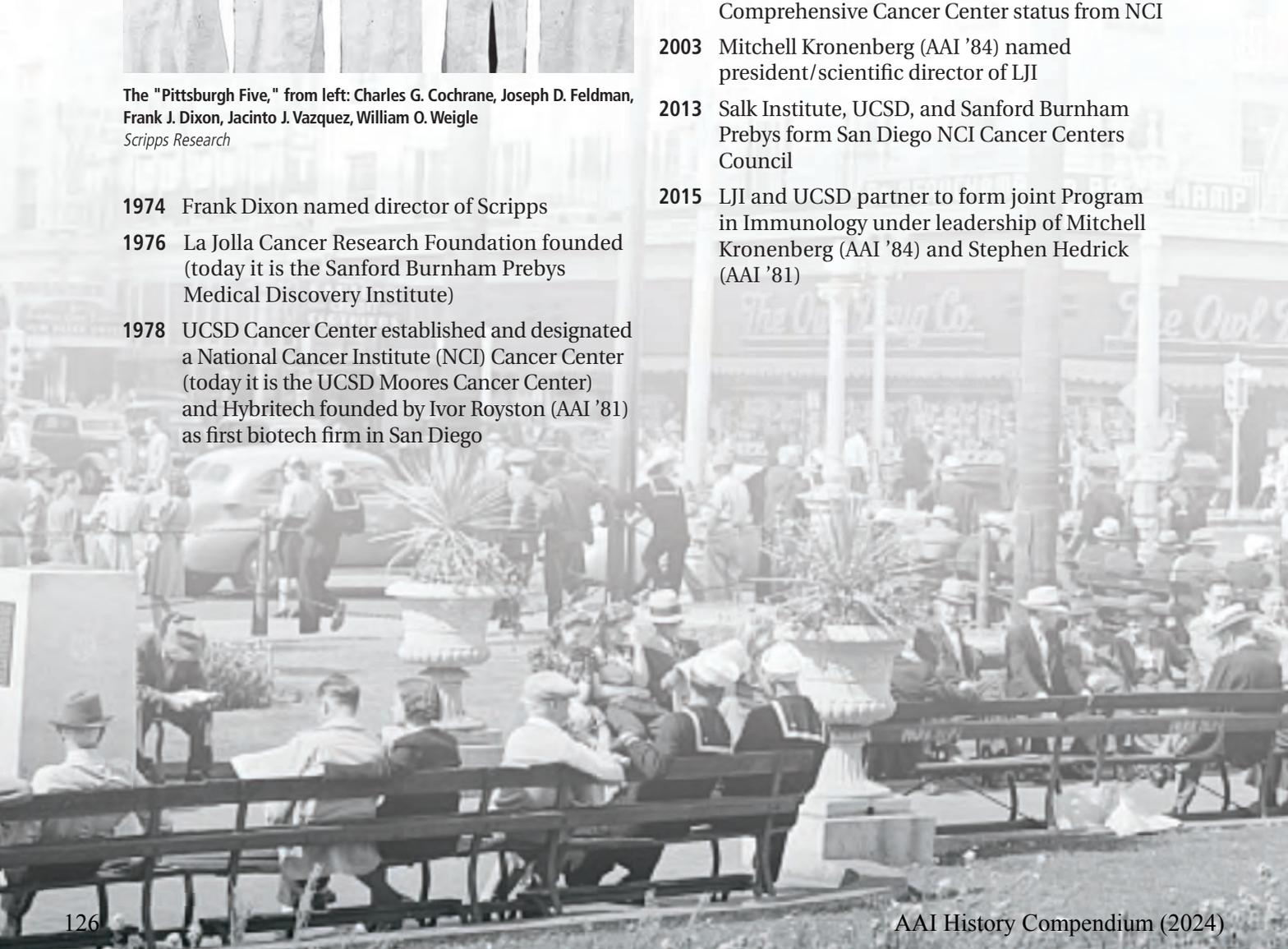


The "Pittsburgh Five," from left: Charles G. Cochrane, Joseph D. Feldman, Frank J. Dixon, Jacinto J. Vazquez, William O. Weigle
Scripps Research

- 1986** Eli Lilly & Co. buys Hybritech for \$413 million
- 1987** Richard Lerner (AAI '68) named director of Scripps
- 1988** Torrey Pines Institute for Molecular Studies founded by Richard Houghten
- 1989** La Jolla Institute for Allergy and Immunology (LJI) begins laboratory operations
- 1991** Kimishige Ishizaka (AAI '58) named president/scientific director of LJI
- 1995** Howard Grey (AAI '65) named president/scientific director of LJI
- 1997** PharMingen begins sponsorship of AAI-PharMingen Investigator Award
- 1999** UCSD Cancer Center receives Comprehensive Cancer Center status from NCI
- 2003** Mitchell Kronenberg (AAI '84) named president/scientific director of LJI
- 2013** Salk Institute, UCSD, and Sanford Burnham Prebys form San Diego NCI Cancer Centers Council
- 2015** LJI and UCSD partner to form joint Program in Immunology under leadership of Mitchell Kronenberg (AAI '84) and Stephen Hedrick (AAI '81)



Kimishige Ishizaka
Kyoto University



The Short and Influential Life of Richard Weil

HISTORY: AAI
PROFILES IN
LEADERSHIP



#10011 PHOTO BY L. SHAPIRO
124th Inf CAMP WHEELER
MACON - GA

Camp Wheeler, Macon, GA, 1917
Library of Congress



Richard Weil
AAI Collection, Center
for Biological Sciences
Archives, UMBC

On November 19, 1917, Richard Weil, an accomplished and highly regarded young physician-scientist and third president of The American Association of Immunologists (AAI), was cut down in his prime by pneumonia at Camp Wheeler, a U.S. Army training facility near Macon, Georgia. In his last weeks, Major Weil had worked tirelessly to fight successive, overlapping epidemics of measles and pneumonia among the World War I draftees, mostly rural and fresh off the train, until he finally succumbed himself. At its next meeting in March 1918, the AAI Council issued a resolution expressing sorrow and honoring Weil for both his “unwearying labors in his chosen field” and his untimely death in the line of duty.¹

Childhood and Education

Born in 1876, Richard Weil came from a well-to-do family with many ties to New York City society and the local Jewish community. Both of his parents had immigrated to the United States from Bohemia in the early 1850s and quickly found comfortable employment. Leopold Weil was a broker at the United States Custom House, and his wife Matilda ran a prominent Jewish girls boarding school. “Mrs. Leopold Weil’s School” educated students from wealthy families all over the country in English, French, German, and Hebrew. Richard was the seventh of eight Weil children who grew up in a series of houses on the Upper West Side of Manhattan that also served at various times as Matilda’s classrooms and as home to her extended family, several student boarders, and a sizable domestic staff.

A gifted student, Weil matriculated at Columbia University where he earned an A.B. at 20 years of age. He immediately continued on to the College of Physicians and Surgeons where he earned his medical degree in 1900.² Upon graduation from medical school, Weil began a two-year residency at the German Hospital in New York City.³ He then travelled to Europe where he continued his training in laboratories and clinics at the universities of Vienna and Leipzig.⁴

Shortly after returning to New York City in 1904, Weil married Minnie Straus, the daughter of Macy’s co-owner Isidor Straus.⁵ His return also coincided with accepting a position at Cornell University Medical College (now Weill Cornell Medicine). He taught



Weil’s father worked as a customs broker at the Merchant’s Exchange Building (now the National City Bank Building) at 55 Wall Street.
Photo ca. 1899–1919.
New York Historical Society

and conducted research there and held concurrent positions at various hospitals in the city from 1905 until 1917, when he enlisted in the U.S. Army.⁶

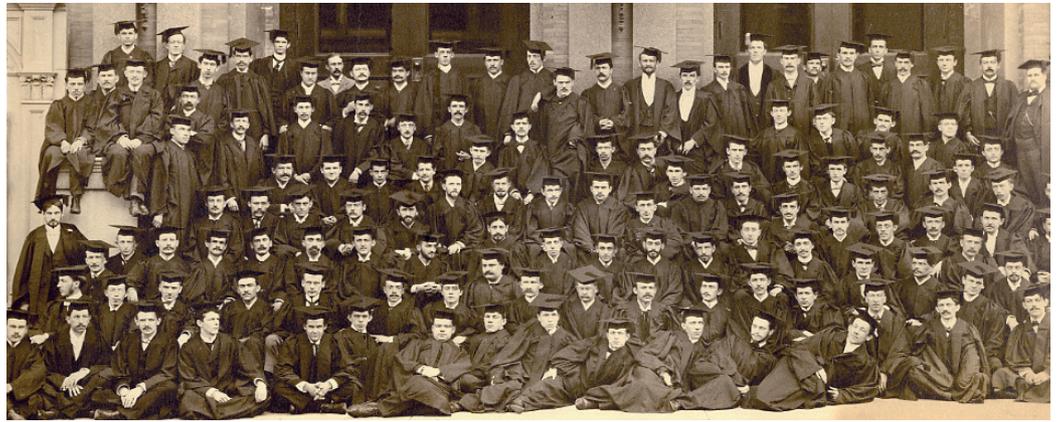
Early Scientific Successes

Upon returning from Europe, Weil's early research in serology quickly gained the attention of scientists in New York City and around the country.

His publications appear diverse—cancer, cobra venom, and blood transfusions—but were fundamentally an exploration of understanding hemolysis. He investigated methods to identify evidence of early stages of cancers circulating in the blood and the effect of cobra venom on human blood, and was the first to demonstrate the feasibility of “icebox” (refrigerated) storage of blood for transfusion.⁷

Cancer, however, was the primary focus of his early research. In addition to his work on devising a blood test for cancer, he examined the hemolytic reactions of cancer, tumor immunology in rats, and the effects of novel experimental cancer treatments including radium. Owing to his investigative work, Weil became a charter member of the American Association for Cancer Research (AACR) in 1907.⁸

By 1912, Weil's focus began to pivot away from cancer towards anaphylaxis. Although he still authored the occasional article on cancer research, the preponderance of his publications until his death related to his ongoing experiments supporting the cellular mechanisms of anaphylaxis. His findings ran counter to the humoral theory then dominating American scientific thought.⁹ His 22-part series on the topic, which only ended upon his enlistment in the Army, proved prescient as discoveries in the 1960s verified the cellular mechanism of anaphylaxis. The series also proved influential to a new field of



Weil's graduation class at the College of Physicians and Surgeons in front of Carnegie Hall, 1900.
Columbia University Irving Medical Center, Archives and Special Collections

science—immunology—as the editors of *The Journal of Immunology* (*The JI*) selected parts 14 through 17 as the first articles published in its inaugural issue.¹⁰

The Beebe Affair

Following his early successes, Weil found himself thrust into the national scientific spotlight when he became embroiled in controversy over a purported cancer treatment at Cornell. In 1915, he was involved in a trial on the validity of “autolysin,” a “liquid extract of vegetable origin” as a

cancer cure.¹¹ The primary investigator of the initial study in 1912 was Silas P. Beebe, a Cornell physiological chemist and a founder of the AACR. Beebe claimed the miracle drug could, with just a few injections, produce “consistent improvement” in inoperable and previously incurable cancers.¹² He also announced—in the pages of the *New York Times*—his intention to move forward with the treatment commercially.¹³

Weil's demonstration that autolysin was not a credible treatment for cancer, coupled with Beebe's push to commercialize the drug, resulted in Cornell asking Beebe to resign from his position as professor of experimental therapeutics, and the department was abolished. Furthermore, scientific societies asked for his resignation or no longer published his science.¹⁴

Following Beebe's departure, Weil found himself the target of numerous inquiries about the promised effects of autolysin. In response, he published a scathing rebuttal in the *Journal of the American Medical Association* (*JAMA*), showing that—contrary to Beebe's



Isidor and Ida Straus with their family in Elberon, N.J., September 1905. Richard and Minnie Weil are on the right.
Straus Historical Society



Silas P. Beebe, ca. 1908
Courtesy of the American
Association for Cancer Research

claims—of 23 patients in the study, 14 died in the hospital, eight were discharged with no improvement, and only one saw any improvement.¹⁵ That patient, like the rest, had also been given Roentgen ray treatment. Out of a job, Beebe was enraged by the challenge and excoriated Weil in *JAMA*, accusing him of “willfully misrepresent[ing]” the study and not “acting solely from good motives.”¹⁶ Because autolysin possessed none of the capabilities Beebe had ascribed to it, Weil emerged from the imbrogl

with increased national credibility as a scientist.

AAI and *The JI*

In addition to his research, Weil offered his service to scientific societies. He was instrumental in recruiting early AAI members and helping select the initial editorial board of *The JI* in 1915.¹⁷ The next year, he became the founding editor of AACR's *The Journal of Cancer Research*, the first English-language cancer journal. Weil also served as the third president of AAI (1916–1917). In keeping with the bylaws at the time, Weil was to serve on the AAI Council until 1924, but when the United States officially joined the First World War on April 6, 1917, he resigned his position and was commissioned as an officer in the U.S. Army Medical Corps.

His first posting at Fort Benjamin Harrison, northeast of Indianapolis, Indiana, was brief. He was quickly promoted to major and detailed to Georgia's Camp Wheeler¹⁸ as the chief of medical staff. At Wheeler, a newly constructed U.S. Army National Guard mobilization and training camp near Macon, Weil experienced a world vastly different—scientifically and socially—from New York City.

The Great War and Camp Wheeler

Camp Wheeler was a temporary 21,000-acre tent camp rapidly built on drained swampland in the spring and summer of 1917. The training camp and mobilization center, which opened in August,¹⁹ housed both white and black men from Georgia, Alabama, Florida, and parts of Virginia.²⁰

Most of the recruits came from rural areas where they were less likely than soldiers from cities to have been exposed to many communicable diseases. At the same time, they were more

likely to be infected by endemic parasites, such as hookworm, that compromised their immune systems.

When Macon's coldest winter in 40 years hit, the Army was unprepared: the men were not equipped with sufficiently warm clothing, the camp lacked winter tents, and conscripts were kept in close quarters at all times to keep warm.

Because of this, Wheeler was presented with significant challenges to preventing communicable diseases, like the flu.

These conditions collectively paved the way for a serious outbreak of measles at the close of 1917. According to Colonel Victor C. Vaughan (AAI 1915), then the chief of the Army's Division of Communicable Diseases, “Not a troop train came into Camp Wheeler... in the fall of 1917 without bringing from one to six cases of measles already in the eruptive stage.”²¹ In addition, 60–70% of recruits were infected with hookworm, which often results in vitamin A deficiency that increases susceptibility to both measles and pneumonia. The measles patients not only had weakened immune systems, but they also were brought together in the hospital tents where their coughs could further spread pneumococcus.²² It was a perfect storm for igniting an epidemic.

Among the approximately 20,000 recruits at the camp,²³ there were 522 cases of measles in October 1917, and 2,421 the next month. In this already compromised population, an epidemic of pneumonia struck next, with 84 cases in October and 452 in November. About a quarter of the men admitted with pneumonia in these two months died. Conditions in the camp were bad enough that in Macon, rumors began flying of dozens of men dying in a single night.²⁴

Weil dedicated himself tirelessly to caring for the sick, but by November 11, 1917, he had fallen ill himself. When word of Weil's illness reached his home in New York, his wife Minnie immediately traveled to Georgia with a specialist from New York to be by his side and assist in his care. Also present on the medical staff was a fellow AAI member, Ernest G. Stillman (AAI 1930), who had been sent to Wheeler to help fight the pneumonia epidemic.²⁵ Weil's condition quickly worsened,

however, and he died after eight days of illness.

The governors of two states made visits to Wheeler to investigate claims of poor medical facilities. Both Governor Hugh Dorsey of Georgia, who toured the camp while Weil lay on his sickbed, and Governor Charles Henderson of Alabama, who arrived the week after Weil's death, found that under Weil, the medical staff had performed admirably.²⁶



Camp Wheeler, 1918
National Archives



Pictured from left: Vaughan, Gorgas, and Welch
University of Michigan, Bentley Historical Library

On November 23, Surgeon General William C. Gorgas, accompanied by William H. Welch and Victor C. Vaughan, arrived at the camp to evaluate the medical situation. By this time, additional medical staff had also been brought in. There were now 280 doctors battling the epidemics at Wheeler. Gorgas explained to a

concerned press that the cause of the measles epidemic was a lack of “resisting power” to the disease among the new recruits from rural areas who had not previously been exposed. He added that “a young man who wants to be a soldier should contrive to have his measles when he is a child.”²⁷

Out of all the U.S. Army camps in 1917, Wheeler had the highest rates of admissions for measles and lobar pneumonia, leading to the second highest death rate in the Army and National Guard.²⁸ To combat epidemics at the camps hardest hit by these diseases, Army medical staff began to keep patients separated in cubicles formed by sheets hung from frames between their beds. This practice proved successful enough that the Surgeon General’s office recommended that it be continued and used more generally—an important innovation when the influenza pandemic hit the next year.²⁹

Influenza

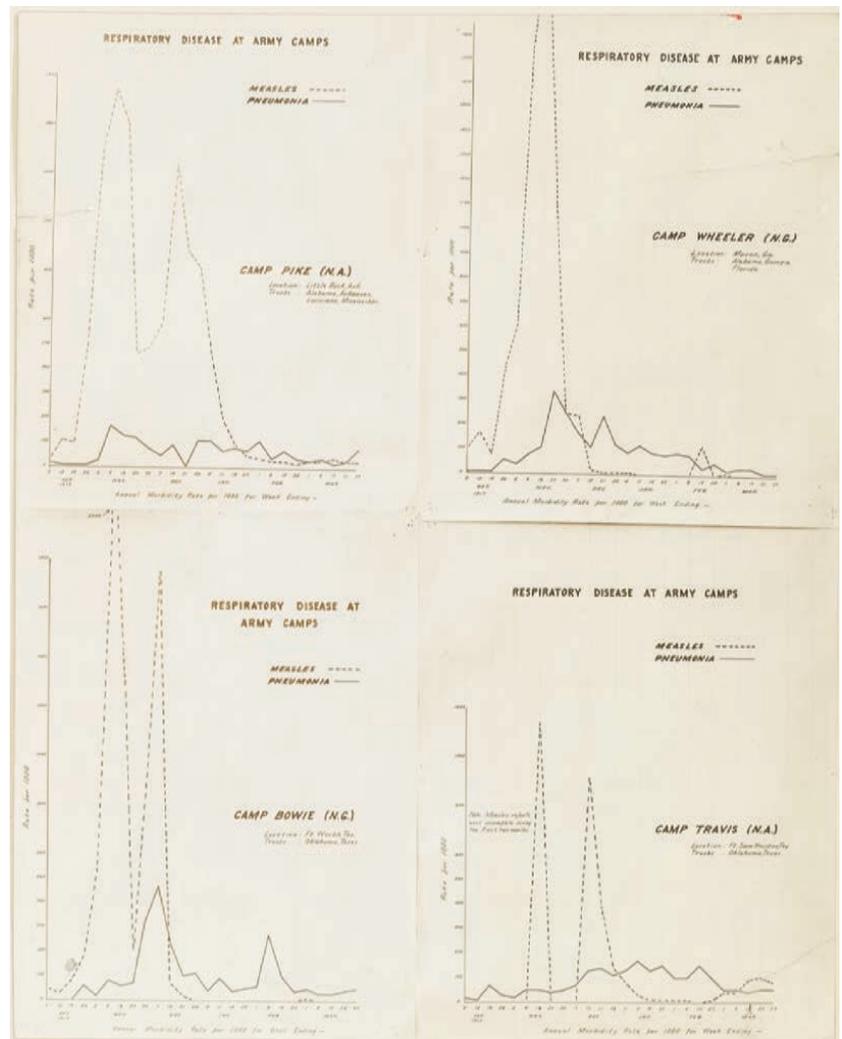
Prior to the outbreak of the pandemic, influenza was not a reportable disease in the general public, but the Army began to track the number of influenza cases among the troops as soon as the United States declared war on Germany in April 1917. Most training camps saw hundreds of unremarkable cases that year, like any other flu season. At Wheeler, there were 685 cases of influenza in the last three months of 1917, but none produced complications and not a single man died.³⁰

The influenza pandemic began quietly on March 4, 1918, at Camp Funston in Kansas, among men from nearby Haskell County.³¹ By April, and half a country away, 1,967 cases of influenza were reported at Wheeler—a few

with complications—but there were still no fatalities from the disease.³² In the late spring of 1918, this initial spike in cases was not seen as the first wave in a global pandemic, but the official report from the Surgeon General described it as an epidemic. When the most significant wave of pandemic influenza came in autumn of 1918, Camp Wheeler was relatively well prepared for it.

Hoping to stave off a repeat of the autumn 1917 pneumonia epidemic, Russel L. Cecil (AAI 1920) and Henry F. Vaughan went to Wheeler in September 1918 to begin a large study on prophylactic vaccination for pneumonia. They vaccinated 13,460 men against pneumococcus Types I, II, and III, and were able to demonstrate an effective immune response before their work was cut short by the appearance of influenza.³³ Notably, their research showed that while overall mortality from pneumonia was significantly lower among those vaccinated, mortality from pneumonia secondary to influenza was unaffected.

Initially, the camp was placed under quarantine following reports of influenza both in the local civilian population and at other military camps. Nationwide, 40,000 cases of influenza among soldiers had been



Army health charts detailing morbidity rates for measles and pneumonia at training camps including Camp Wheeler, October 1918–March 1919
National Archives

reported by the end of September. Up to that point, Wheeler was publically considered free of influenza, but on the 28th of the month, camp officials acknowledged that their first cases had been admitted to the base hospital.

The lessons learned in the measles and pneumonia epidemics of 1917 seem to have had a positive effect on Wheeler's preparedness for pandemic influenza. Having already experienced one of the worst battles with communicable disease among all the Army camps, Wheeler's medical staff was practiced at identifying and isolating patients who displayed dangerous symptoms.

Exact comparisons to other camps are unfortunately impossible; unlike their counterparts at the vast majority of Army camps, Wheeler's physicians made an official diagnosis of influenza only upon a laboratory finding of Pfeiffer's bacillus (*Haemophilus influenzae* [then known as *Bacillus influenza*]), at the time thought to be the cause of influenza. Because the bacterial infection does not always present in every instance of influenza, this practice would have ignored many actual cases of the disease.

Even with this administrative discrepancy, however, the records show that Wheeler experienced significantly lower than average rates of admission and death for all respiratory diseases in 1918.

Tribute to Richard Weil

Richard Weil's funeral was held with military honors at Temple Emanu-El in Manhattan on November 23, 1917. The respect the young physician-scientist commanded among his peers



Temple Emanu-El, 5th Ave. and 43rd St., ca. 1860s
Temple Emanu-El

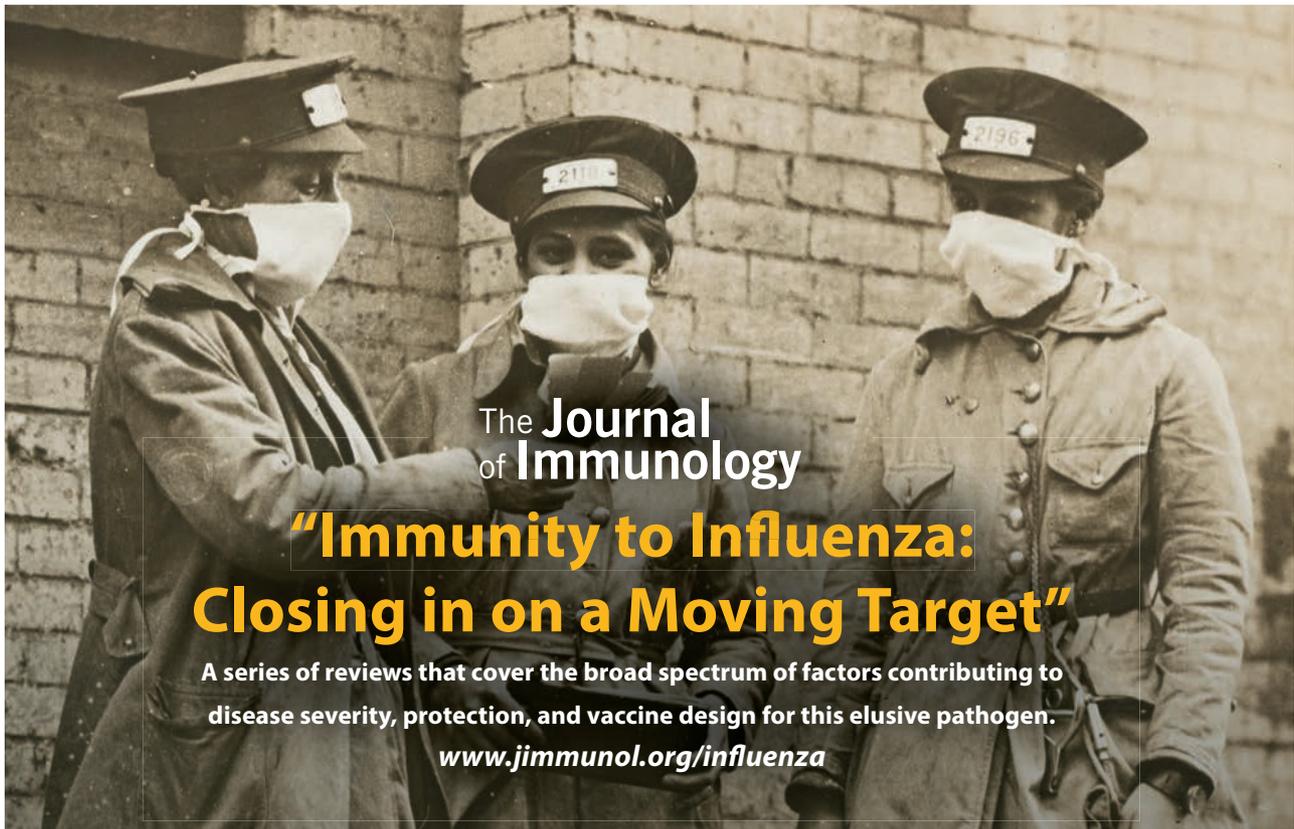
was evident in the men who served as his honorary pallbearers. They included Rufus Cole (AAI 1917, president 1920–21), director of the Rockefeller Institute; William M. Polk, dean of the medical school at Cornell; William B. Coley, father of cancer immunotherapy; and Arthur F. Coca (AAI 1916, *The JI* editor-in-chief 1916–48); as well as several other prominent physicians, scientists, businessmen, and bankers.

Weil is remembered for his remarkable and selfless service to his country and his seminal contributions to the field of immunology. His service during World War I and his efforts to address Camp Wheeler's medical problems demonstrated the important role immunologists played during this challenging period.

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- 2 As the son of Jewish immigrants, Weil was fortunate to get his education before Columbia and many other U.S. universities instituted restrictive quotas that limited the number of Jewish students in the early 20th century.
- 3 The German Hospital was renamed Lenox Hill Hospital in 1918 to tie it to its location as well as distance it from any association to Germany during World War I.
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- ²⁰ Although the male-only draft for World War I was universal and included African Americans, the U.S. Army was segregated, as were the other branches of the U.S. military, and so were the training camps and mobilization centers.
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Hidden Figures of AAI: Five Women Pioneers in Immunology

HISTORY:
WOMEN IN
IMMUNOLOGY



Pictured from left: Drs. Wollstein, Povitzky, Ashby, Bliss, and Marmorston

AAI is dedicated to preserving the historical accounts of women who influenced the field of immunology. Thank you to John Emrich, Ph.D., and Charles Richter, M.Phil., of the AAI Office of History for their tireless research for and preparation of this article.

At the 1908 annual meeting of the Women's Medical Society of the State of New York, Martha Wollstein (AAI 1918), the pathologist at Babies Hospital, gave a speech entitled "The History of Women in Medicine," highlighting women's progress and setbacks in the field since the time of the ancient Greeks. Wollstein's conclusion was a call to action advocating for more opportunities for women in all aspects of medicine. She declared that the current generation was the first to have "entered societies and laboratories for the benefit of all."¹

Wollstein spoke in an era when women in science and medicine were viewed by many in the scientific community as inferior to their male counterparts. They were not generally provided the same rights and privileges as men in the laboratory or clinic. Medical societies typically banned women or elected only a token few, sometimes to a lower member status than men. By contrast, from the time of its founding five years after Wollstein's speech, The American Association of Immunologists had no gender restrictions, and women and men alike were elected as full members.

To mark Women's History Month in March 2020, we profile five women immunologists who in the early decades of the 20th century persevered in the fields of bacteriology, serology, public health, pediatric pathology, and drug development. They moved the science of immunology forward while simultaneously opening the field to future female immunologists. These pioneers are Martha Wollstein (AAI 1918), Olga R. Povitzky (AAI 1920), Winifred M. Ashby (AAI 1923), Eleanor A. Bliss (AAI 1931), and Jessie Marmorston (AAI 1932).

These women were at very different career stages when they joined AAI; most were immigrants or first-generation Americans, and all were accomplished immunologists. Given gaps in the historical record, they also represent other trailblazing women scientists of their era whose lives and accomplishments have been lost to history.

Martha Wollstein, M.D. (1868–1939)

Martha Wollstein (AAI 1918) was an accomplished physician, researcher, and the "first North American pediatric pathologist" when she became one of the first women elected to active AAI



Babies Hospital, c. 1876–1914
New York Historical Society

membership in 1918.² She was born in New York City on November 21, 1868, to German Jewish immigrant parents who encouraged her education. Wollstein received her M.D. in 1889 from the Woman's Medical College of the New York Infirmary,³ interned at Babies Hospital,⁴ and in 1891 was appointed its pathologist—a unique position for a woman of that time because it allowed her to practice the full scope of pathology, including patient care, bench research, and autopsies.

Her clinical and basic research at Babies Hospital included malaria, tuberculosis (TB), and typhoid fever. But it was her investigation of the bacterial causes of infant diarrhea that first caught the attention of the scientific community, including Simon Flexner (AAI 1920), the recently appointed first director of the

Rockefeller Institute for Medical Research (RIMR). In 1903, Wollstein isolated Shiga bacillus, which only three years prior had been shown to cause dysentery, in some of her patients.⁵ Flexner, whose research focused on dysentery in the Philippines,⁶ was so impressed by her research that he offered her a position as an assistant researcher at RIMR in 1906.

In her concurrent position at RIMR, most of Wollstein's research was non-pediatric in nature, with the exception of polio research with Flexner.⁷ She maintained her duties and pediatric research at Babies Hospital, including publishing an important, three-part series on the incidence and clinical effects of TB in babies. This was the first study to provide data specific to childhood TB.⁸



Rockefeller Institute for Medical Research Lab Staff (Wollstein middle row, first on left)
Rockefeller Archive Center



Postcard of Women's Medical College of Pennsylvania, 1906

At RIMR, her significant collaborations included developing methods and protocols to create anti-meningitis serum with Harold Amoss (AAI 1917)⁹ and streptococcal and bronchopneumonia studies with Samuel J. Meltzer. The latter collaboration would influence measles researchers generally, and the streptococcal research would become the life's work of one of her successors at RIMR: Rebecca Lancefield (AAI 1931, president 1961–62).¹⁰

With the outbreak of the influenza pandemic of 1918, Wollstein became intimately involved with the influenza research at RIMR because of her earlier research on the development of a Pfeiffer's bacillus serum.¹¹ At the time, Pfeiffer's bacillus (today known as *Haemophilus influenzae*) was considered widely to be the causative agent for influenza,

although new studies were beginning to question the accuracy of this belief. Wollstein's work provided additional evidence that the prevailing hypothesis was incorrect and that the bacillus was a secondary infection.¹²

Wollstein's core research remained focused on childhood diseases, and in the late summer of 1918, she published her most influential discovery on the etiology of mumps.¹³ The popular medical consensus held that a type of coccus was the causative agent of mumps because it was isolated from the blood, saliva, and fluid aspirated from the swollen parotid gland. Wollstein's research definitively concluded that mumps was not bacterial but viral in nature.

In 1921, after RIMR did not extend an offer to her to join the staff on a permanent basis, she returned full time as the pediatric pathologist at Babies Hospital and devoted her research to pediatric diseases, including leukemia, TB, influenza, and meningitis.

During her career, Wollstein published more than 60 scientific papers and won numerous honors, including an appointment as head of the pediatric section of the New York Academy of Science (1928) and election to the American Pediatric Society (1930) as its first female member.¹⁴

Olga Povitzky, M.D. (1877–1948)

Olga Raissa Povitzky (AAI 1920) had a 41-year research career with the New York City Department of Health—remarkable for a woman who came to Philadelphia from Lithuania as a 16-year-old girl on her own, speaking only Russian.

Povitzky joined her older brother Charles, a druggist who had immigrated two years earlier.¹⁵ She learned both English and medicine at the Women's Medical College of Pennsylvania (now part of Drexel University College of Medicine).¹⁶

She managed to overcome the language barrier, but later recalled an incident in which she was asked what she thought of a lecture on Darwin and replied—without meaning to make a pun—“I did not understand it very well but there seemed to be a lot of monkey business in it.”¹⁷

Povitzky completed her M.D. in 1901 and briefly maintained a private practice in Mahanoy City, Pennsylvania, before moving to New York City, where she spent the rest of her life. She became a U.S. citizen in 1904. She earned a doctorate in public health from New York University (NYU) in 1905 and that same year began her research in the Health Department laboratories, initially working on equine glanders, a contagious bacterial infection that created nodular legions primarily in the lungs and skin.¹⁸ She was also an active lecturer on public health at NYU.

Povitzky was politically active, donating to the socialist magazine *The New Review* and advocating for women's suffrage. During the First World War, she joined the first contingent of the Women's Oversea Hospitals, sponsored by the National American Woman Suffrage Association. In February 1918, she set sail for the war zone in France with a group of 30 other women that included nurses, a plumber, a carpenter, a chemist, drivers, and five other physicians.

The male French military surgeons initially viewed the women with suspicion, but only briefly. A day after their arrival at the field hospital, it was suddenly flooded with 650 wounded from a German advance. The women “did not stand on their dignity but did whatever needed to be done,” including cutting off bloody bandages, giving injections, and preparing wounded soldiers for surgery. Povitzky was then sent to the Pasteur Institute in Paris to receive specialized training in gas gangrene. She spent the rest of the war at the Laboratoire d'Epidemiologie at Le Mans “doing all the bacteriological, physiological, and chemical examination for the military hospitals of Sarthe, Mayenne, Eure et Loire and Orne.”¹⁹

After the war, Povitzky returned to the New York City Department of Health, where for several years she oversaw the manufacture of diphtheria antitoxin in the laboratory of William H. Park (AAI 1916, president 1918–19). She also studied *H. influenzae*, experimenting with a serum that could cure meningitis caused by this bacterium.²⁰ Throughout the 1920s and 1930s, she published in *The*



First Contingent of Women's Oversea Hospitals, c. 1918 (Povitzky front row, third from right)
National Archives

*Journal of Immunology*²¹ and other journals, primarily on developments that refined production techniques for diphtheria toxoid and antitoxin, and also on pertussis.

In the 1930s, Povitzky designed a rectangular two-liter Pyrex culture bottle for diphtheria antitoxin production that was later adopted in a larger five-liter size as the standard vessel for the Salk polio vaccine. The durable “Povitsky bottle” proved ideal for culturing poliovirus in a custom-made rocking rack.²²

She remained active in the laboratory until just two years before her death in 1948.

Winifred Ashby, Ph.D. (1879–1975)

Winifred M. Ashby (AAI 1923) made her imprint on immunology while conducting research for her Ph.D. dissertation.²³



Winifred Ashby
National Library of Medicine

This work led her to develop the first technique to determine red blood cell lifespan in humans. The Ashby technique (or Ashby method) was a major step in increasing the efficacy of blood transfusions and the management of chronic anemia. The technique saved countless lives during World War II because it was the primary



A chemistry laboratory in St. Elizabeths Hospital, c. 1910
National Library of Medicine

method to assess the storage and shipping of blood for transfusion required for the war effort. By the late 1960s, the Ashby technique of differential agglutination was replaced by radioisotope-tagging of red blood cells, which was safer, easier, and provided a higher degree of precision and accuracy.²⁴

Ashby and her family emigrated from England to Chicago when she was 14. She earned her B.S. from the University of Chicago (1903) and an M.S. from Washington University in St. Louis (1905). While at Washington University, Ashby became interested in immunology, but did not immediately enter the field. Instead, over the next 12 years, she travelled to the Philippines to study malnutrition, taught high school physics and chemistry, and worked in laboratories at Rush Medical College and the Illinois Central Hospital. In February 1917, she began a Mayo Foundation fellowship in immunology and pathology.²⁵

Her research at the Mayo Foundation tested the widely accepted theory that the lifespan of an average human erythrocyte was two to three weeks. Ashby set out to determine the lifespan of transfused red blood cells in patients, adopting the technique that would come to bear her name. It was based on the fact that type AB, A, or B blood cells (Group I, II, and III in her terminology) will agglutinate when treated with serum from a person of another blood type, while type O blood cells (Group IV) lacking ABO antigens will not agglutinate.

Ashby transfused patients of blood type A, B, or AB with type O blood and then treated blood specimens *in vitro* with anti-A or anti-B serum, which would agglutinate the blood cells of the patient but not those of the blood donor. She determined that counts of unagglutinated cells from the specimens correlated with the number of transfused blood cells present in the recipient's circulation, and that the transfused cells could persist for 30 days or more.²⁶ Further research proved that a red blood cell could circulate for up to 110 days.²⁷

Following her graduation from the University of Minnesota in 1921, Ashby became a researcher in the division of experimental bacteriology at the Mayo Foundation; in 1923 she became a member of the Mayo Clinic staff.

In 1924 Ashby accepted a position as an immunologist at St. Elizabeths Hospital in Washington, D.C., where she supervised the serology and bacteriology laboratories. While at St. Elizabeths, Ashby's research initially focused on immunology, pathology, and hematology. Later in her career, she also studied brain and central nervous system enzyme chemistry, notably carbonic anhydrase and patterns of enzyme distribution in brain functions.

She officially retired in 1949, though she remained at St. Elizabeths as a guest researcher until 1958.²⁸

Eleanor Bliss, Sc.D. (1899–1987)

The research that **Eleanor Albert Bliss (AAI 1931)** performed with sulfanilamide drugs saved the lives of countless soldiers



Eleanor Bliss, 1942
Richmond Times Dispatch; Newspapers.com

in World War II, as well as that of the U.S. president's son. Her work with fellow Johns Hopkins University professor Perrin H. Long uncovered numerous uses for the sulfa compounds and launched antibacterials into the public consciousness.

Bliss grew up in Baltimore and attended Bryn Mawr College, receiving her A.B. in 1921, and then continued to Johns Hopkins where she earned her Sc.D. in

1925. She immediately joined the Hopkins faculty as a fellow in medicine. Early in her career, she worked on influenza and whooping cough but soon turned her attention to fighting streptococcal infections. In 1934 she and Long isolated minute beta hemolytic streptococci that would be classified as the Lancefield group F.²⁹

Bliss's scientific epiphany came when she traveled to London in July 1936 to attend the Second International Congress of Microbiology. There, she learned of Leonard Colebrook's (AAI 1915) first clinical study to treat haemolytic streptococcus using the recently created sulfa drug Prontosil. Colebrook's research proved that Prontosil

was the first synthetic drug to effectively treat a range of bacterial infections in humans and rendered a particularly strong response to streptococcal infections.³⁰ Bliss and Long immediately requested samples of Prontosil for their own research, and by that September had successfully treated a seven-year-old girl for erysipelas (a streptococcal infection of the skin and superficial lymphatics) with *p*-aminobenzenesulfonamide (PABS, or sulfanilamide), one of the intermediate molecules of Prontosil.

That November, Bliss and Long presented their preliminary findings at the meeting of the Southern Medical Association in Baltimore. In December, the team achieved its first successful treatment of streptococcal meningitis, which previously had a nearly 100% mortality rate.³¹ Days later, front-page news broke that the president's son, Franklin Delano Roosevelt Jr., had also been cured of a lethal streptococcal infection using a treatment based on Bliss and Long's findings.³² Within months, several clinical trials demonstrated the drug's efficacy against a broad range of infections.

The next year, Bliss defended the proper use of sulfanilamide after the S. E. Massengill Company produced an "Elixir of Sulfanilamide" that contained toxic diethylene glycol, resulting in more than 100 deaths in 15 states. The direct result of the tragedy was the 1938 Federal Food, Drug, and Cosmetic Act, which established more stringent safety standards for drug production and sales.³³



Tube of Prontosil tablets, c. 1935–1950
Science Museum, London

The Second World War proved the importance of Bliss's work. Sulfa drugs were used extensively on the battlefields and in military hospitals to treat and prevent infection and were included as part of the standard issue first-aid kit.³⁴ Toward the end of the war, Bliss served as an advisor to the U.S. Army Chemical Corps (then called the U.S. Chemical Warfare Service) on defenses against biological weapons.³⁵

Bliss remained on the faculty at Johns Hopkins until 1952, when she returned to her alma mater Bryn Mawr as professor of biology and the graduate dean. She remained there until her retirement in 1966.

Jessie Marmorston, M.D. (1900–1980)



Jessie Marmorston, 1951
National Library of Medicine

From an early age, **Jessie Marmorston** (AAI 1932) spoke her mind and excelled at practically everything she set out to do. Born in Kyiv (then part of the Russian Empire), she arrived in the United States with her family in 1906 and settled in Buffalo, New York. Her mother's death the next year inspired her to become a doctor.³⁶ She had her first job in medicine at a dentist's

office when she was only 10 years old.³⁷ As a teenager, Marmorston was active in theater and debate clubs—and known as “an enthusiastic and wordy suffragette.”³⁸

The powers of persuasion she developed in her youth proved useful when she convinced the Buffalo Federation of Mothers to set aside funds for her university and medical school tuition.³⁹ She graduated from the University of Buffalo with a pre-med degree and earned her M.D. (1924) from the University of Buffalo School of Medicine, followed by an internship at Montefiore Hospital in the Bronx, New York City.

There she met David Perla, also an intern, and their shared love of immunology turned into a scientific partnership. Marmorston moved to Cornell University Medical College and was briefly married to Julius Gottesman, another physician, but her professional relationship with Perla continued, eventually developing into her second marriage. The couple published two well-received books on their research before Perla died prematurely of a sudden heart attack in 1940.⁴⁰

Through Perla's social network, Marmorston had made some connections within the Hollywood film industry, and in 1943 she moved west to take a position as assistant professor of medicine at the University of Southern California (USC). Two years later, she married film producer Lawrence Weingarten, who would eventually produce *Cat on a Hot Tin Roof*. She also became the personal physician and confidante of Louis B. Mayer, the co-founder of Metro-Goldwyn-Mayer studios.

Marmorston used these Hollywood connections to generate funding for scholarships at USC; in 1959 she



Marmorston (second from right) with Clayton G. Loosli (far left), dean of the USC School of Medicine, and members of men's and women's committees for the *Ben-Hur* premiere performance at the *Ben-Hur* Premiere Benefit, 1959
 University of Southern California

arranged a benefit screening of *Ben-Hur* that resulted in more than \$100,000 in donations in a single night.⁴¹ The next year, she was elected a Fellow of the American College of Physicians and named one of 10 Women of the Year by the *Los Angeles Times*.⁴²

Socializing with filmmakers did not slow the pace of Marmorston's research in Los Angeles. Supported by several grants from the United States Public Health Service and the National Institutes of Health, she continued to publish extensively on hormonal mechanisms and their possible applications for treating cancer, heart disease, and other conditions—including those related to the aging process.

Her research also explored links between mental health and the immune system.

Marmorston stayed at USC for the rest of her professional life, becoming professor of experimental medicine in 1953 and clinical professor of medicine in 1957. In addition to her research, she served as the supervising director of the California Foundation for Medical Research and as an attending physician at Cedars-Sinai Hospital and Los Angeles County Hospital. She was a consistent advocate for greater opportunities for women in the medical and research professions.⁴³

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Learn more about the female trailblazers of immunology, past and present, at www.aai.org/WomeninImmunology.



How Honolulu's Chinatown "Went Up in Smoke"

The First Plague Outbreak in Hawai'i, 1899–1900



Kaumakapili Church after the fire, 1900
Hawaii State Archives

IMMUNOLOGY2020™ was to have featured a history exhibit exploring the interplay between immunology and public health in Hawai'i, including a retrospective on the 1899–1900 bubonic plague quarantine in Honolulu. Following the unfortunate cancellation of the AAI annual meeting due to public health restrictions during the COVID-19 pandemic, the History Office of AAI is pleased to present the following, expanded version of the exhibit for members and other readers of the AAI Newsletter.

Bubonic plague (*Yersinia pestis*), responsible for the worst pandemics in history, was unknown in Hawai'i until the last days of the 19th century. When it appeared there, local government health authorities reacted swiftly and severely. The resulting quarantines and public health measures turned into a local disaster and a tragedy for Honolulu's large Chinese population.

The Third Plague Pandemic

When a plague outbreak began in China in 1860, triggering the world's third plague pandemic, experience from previous outbreaks in other parts of the world demonstrated that the disease was more than a substantial health threat; it was one that conveyed terror of historic proportion. Death from the disease was inevitably painful and gruesome, and depending on the virulence of the strain, fatality rates could range from 35% to 90%. The populations previously struck by pandemic bubonic plague had experienced mortality rates so high that it was difficult to count the total deaths.

The Plague of Justinian (biovar *Antiqua*) occurred from 500 to 700 CE, peaking in 541–542, and resulted in 25–100 million deaths. The Black Death (biovar *Medievalis*), which occurred during the 14th century, peaked between 1347–1351 in Europe and resulted in 75–200 million deaths in Asia, North Africa, the Middle East, and Europe.

As news of the emerging outbreak in China began to spread, public health officials around the world became alarmed,

particularly those in Asia and the Pacific Islands. By the mid-1890s, the third plague pandemic was well underway, traveling via overland and shipping trade routes to countries around the globe, including Hong Kong, India, Egypt, Japan, South Africa, France, Great Britain, and Australia.¹

This pandemic, however, provided researchers the ability to study the plague at the microscopic level for the first time. In 1894, bacteriologists Shibasaburo Kitasato and Alexandre



Chinatown before the fire
Hawai'i State Archives

Yersin traveled to Hong Kong to study the plague outbreaks in Asia and—independently of one another—managed that year to identify the bacillus responsible for the disease.² A year later, Paul-Louis Simond, a Pasteur researcher in Bombay, India, demonstrated that fleas were the vector that transmitted the plague bacterium.

Precautions in Hawai'i

The growing threat of plague outbreaks led the Hawaiian government (see sidebar pg. 34) to intensify inspections of all ships in Chinese and Japanese ports bound for Hawai'i. Sand Island in Honolulu Harbor became "Quarantine Island," where all ships from ports where outbreaks had occurred were held for a week.³ Initially, the measures proved effective: although plague spread throughout other Pacific islands, Hawai'i remained apparently safe.⁴

Unknown to nearly everyone in Honolulu, however, plague quietly arrived in the city's harbor in June 1899 on the Japanese passenger liner *Nippon Maru* bound for San Francisco. The first signs had been detected at the ship's first stop in Nagasaki, where a teenage passenger died on May 26. He had no outward signs of disease, but Japanese medical officers made a diagnosis of bubonic plague by visual examination of his glands under a microscope.⁵ The *Nippon Maru* was then held in a week-long quarantine, during which the ship was washed with carbolic acid and all its contents steamed. Only after the decontamination was it allowed to continue its voyage to Honolulu.

Another passenger died on the approach to Hawai'i, and upon the vessel's arrival, the Hawaiian government's bacteriologist found "considerable numbers of a short bacillus, rounded at both ends, and like the bacillus of bubonic plague."⁶ No cargo was allowed off the ship, mainland-bound passengers were not permitted to disembark, and the few Honolulu-bound passengers were transferred to a separate quarantine ship. However, no efforts were made to prevent rats from escaping the quarantined ship. Health authorities in Honolulu decided not to make this case public.⁷

Chinatown, Honolulu

Chinese visitations to Hawai'i date to the late 18th century, when Chinese sailors arrived in the islands along with the earliest European and American explorers and traders. The

first permanent residents came in 1823 and, by 1840, 10% of the 400 foreigners living in Honolulu were Chinese. The rise of the sugar industry in the 1850s brought a new wave of Chinese laborers seeking work on the plantations. Most did not work the sugar fields for long; they found work on smaller farms or went into business for themselves. By 1884, 18,254 Chinese residents made up 22.7% of Hawai'i's population and represented the largest non-Hawaiian ethnic group in the islands.⁸

Most Chinese in Honolulu lived and worked in the city's Chinatown, a 14-block neighborhood bordered by Honolulu Harbor to the west, Nu'uuanu Stream to the north, and downtown Honolulu to the south. It was a densely populated district, home to approximately 7,000 people and many Chinese- and Japanese-owned businesses by the turn of the century.⁹

Plague and Quarantine in Honolulu

The first case of the flea-borne disease emerged when You Chong, a bookkeeper in Honolulu's Chinatown, fell ill on December 9, 1899, and developed telltale buboes before dying three days later. Four neighbors succumbed quickly

thereafter. By that time, plague had likely been spreading quietly among the local rat population for months. Unfortunately, although the bacillus had been identified five years earlier, still very little was understood about how it behaved.¹⁰

On December 13, Honolulu newspapers announced the threat of plague and asked for volunteers to report to the Territorial Board of Health (BoH) to begin inspections of

properties.¹¹ Two days later, they confirmed that several people had indeed died from plague. The BoH closed inter-island ship traffic, sealed off Chinatown, and restricted travel in and out of Honolulu. A corps of volunteers began inspections to find any additional cases. Believing that plague germs could live inside walls, under floors, and amongst personal belongings, they sprayed premises with various disinfectant solutions, including sulfuric and carbolic acids.¹² When no further cases were found for a week, the quarantine was lifted on December 19.

A Second Wave and Quarantine

The week of Christmas, however, brought at least four new cases of plague. The BoH blamed the residents of



Cordon sanitaire of Chinatown, c. Dec. 1899 – Jan. 1900
Hawai'i State Archives



Belongings in the street; *cordon sanitaire* at end of street, c. Dec. 1899 – Jan. 1900
Hawai'i State Archives

Chinatown for the outbreak, reflecting long-held racist stereotypes about their standards of cleanliness or the foods they ate.¹³ The board also distributed a multi-lingual pamphlet promoting cleanliness and citing Kitasato's research on plague.¹⁴ By 3:00 AM on December 28, National Guard troops enforced a *cordon sanitaire*—a literal rope barrier in the streets—to prevent 10,000 people from leaving the 14-block Chinatown neighborhood.¹⁵ News of the situation was slow to arrive to the mainland: on December 30, while the new quarantine was in effect, stateside newspapers proclaimed that “bubonic plague has been stamped out in Honolulu.”¹⁶

Sanitary Fires

The situation took an ever-darker turn when the BoH, frustrated by the pace of abatement and hoping to re-open Honolulu more quickly, began setting fire to homes and businesses where plague was found. For the first three weeks of January, buildings were destroyed by “sanitary fires” every day. Readers of the *Honolulu Advertiser* could track the intentional demolition of Chinatown through maps updated daily to show which blocks had been burned or marked for burning.

Inferno

This tactic took a disastrous turn on January 20 when strong winds blew flying embers from one of the fires onto the wooden steeples of the recently constructed Kaumakapili

Church.¹⁷ As if a spark had landed in a tinderbox, the gothic church quickly burned to the ground and flames spread to neighboring buildings. The out-of-control Chinatown inferno generated heat so intense it melted metal cookware, but the citizen guards wielding axe handles insisted on maintaining the quarantine line until the fire forced everyone to flee.¹⁸ The blaze destroyed 60 acres of Chinatown and the surrounding neighborhoods, leaving more than 4,000 people homeless and only five gutted buildings standing.¹⁹

Even after the fire was extinguished, the BoH continued to set controlled burns in the emptied district, fortunately with no further conflagrations.²⁰ With the horrific failure of the quarantine measures, authorities placed the former residents of Chinatown into detention camps to minimize the spread of the disease. Cases nevertheless continued to appear for the next two months, including on the big island of Hawai'i.²¹ Ultimately, the BoH reported that the Honolulu plague outbreak produced a total of 71 diagnosed cases and 61 deaths through March 31, 1900.

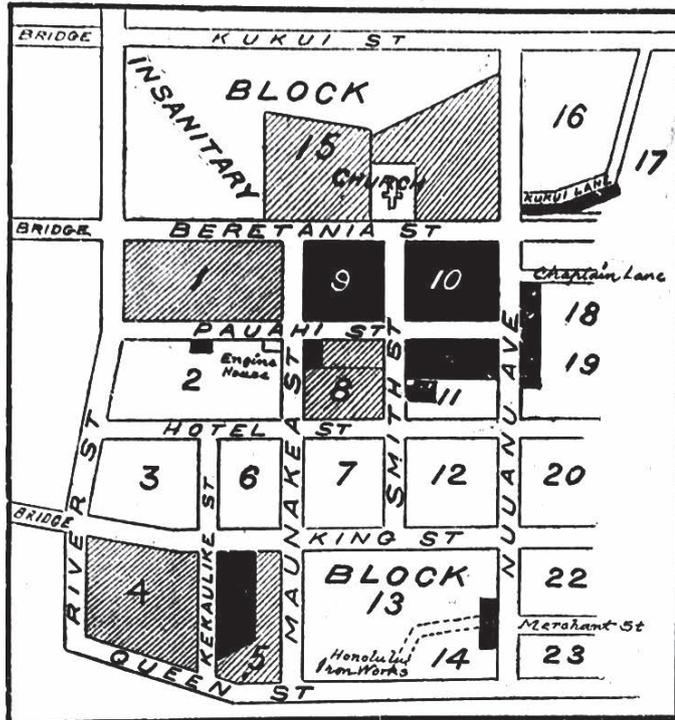
Plague Reaches the United States

Just after midnight on March 6, 1900, bubonic plague arrived in the continental United States. In San Francisco, the dead body of Chick Gin, a 41-year-old Chinese laborer, was discovered in the basement of the Globe Hotel, a run-down boarding house in Chinatown. This discovery set in motion public health measures, including quarantines; *cordon sanitaire*; intensive disinfecting efforts that included burning personal property; and racist stereotypes that were similar, if not more pronounced, than those that recently

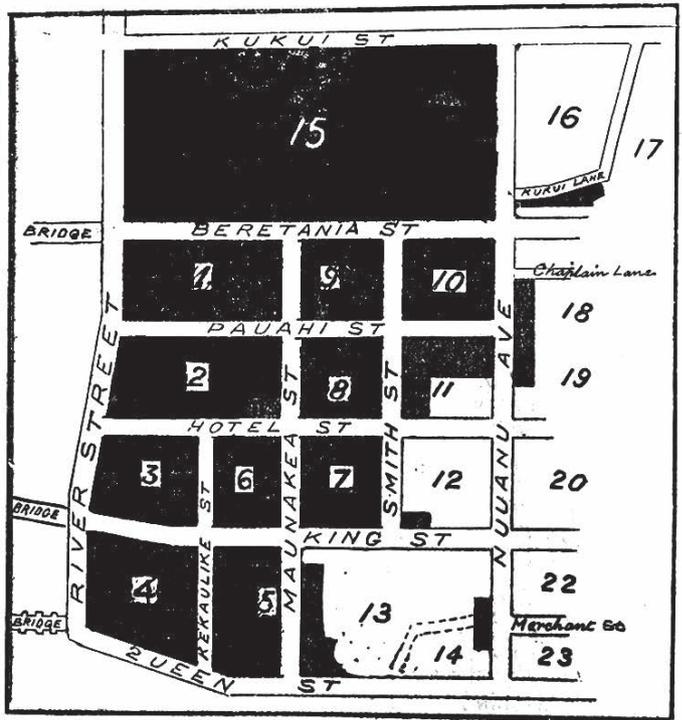


Fighting the fire in Chinatown, Jan. 1900
Hawai'i State Archives

THE PASSING OF CHINATOWN.
(Map Changed Daily.)



THE PASSING OF CHINATOWN.



"The Passing of Chinatown" before (January 20) and after (January 24) the fire, *Honolulu Advertiser*, 1900
Hawai'i State Archives

ended in Honolulu. It also led to the establishment of a federal plague laboratory in 1903, which would become home to a number of future AAI members and their research over the next few decades.²²

George McCoy and Anti-plague Efforts in Hawai'i

In October 1911, George W. McCoy (AAI 1915, president 1922–23) arrived in Hawai'i to lead the Leprosy Investigation Station, but he also brought with him years of experience with plague.

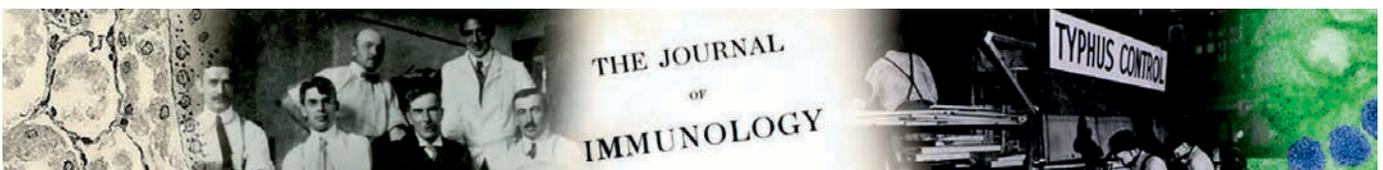
Shortly after the 1899–1900 Honolulu plague outbreak, McCoy had been sent to the Philippines to serve as a quarantine officer on his first assignment with the U.S. Public Health Service (PHS). In the Philippine Commission's annual report to the PHS, McCoy described his frustration with the ineffective policies employed against diseases such as cholera.²³ He was later assigned to postings in China and Japan, where he served as one of the inspectors checking

ships bound for Hawai'i for indications of plague, and then to the Plague Laboratory in San Francisco, which he led from 1908 until his posting to Honolulu in 1911.²⁴

Plague had continued to show up occasionally in the rural areas of the Hawaiian Islands, so McCoy instigated a survey of cases both prior to his arrival and during his tenure there. His findings showed that the disease was not limited to any ethnic group; the victims were ethnically and economically diverse.²⁵ Large-scale rodent reduction efforts resulted in the capture and extermination of tens of thousands of rats and mice. From 1910 to 1913, one in every 1,442 rodents examined was found to be infected with plague.²⁶

A New Concept in Plague Transmission

By the 1930s, the concept developed by Karl F. Meyer (AAI 1922, president 1940–41) of a rodent population acting as a reservoir of disease had yielded to more effective plague abatement techniques,²⁷ which were employed in Hawai'i by the PHS and BoH to successfully reduce rat populations and, consequently, potential human exposure to plague.²⁸



Want More AAI History?

Visit www.aai.org/history for the AAI Timeline, which chronicles 100 years of immunology history, more articles, the Oral History Project, and more.

A Chronological Overview of Hawai‘i and Public Health

Epidemic diseases have devastated the native population of Hawai‘i since 1778, when Captain James Cook first landed in the islands. Centuries of isolation meant that Hawaiians were particularly vulnerable to diseases from all over the world. Estimates of the native population in 1778 range from 300,000 to nearly 700,000. Just 40 years later, the figure had dropped to about 150,000, and by 1900, to only 28,800. Aggressive public health measures prevented an even worse decline, and today the Native Hawaiian population has returned to nearly 300,000.

Since first contact with Europeans, the islands became a strategic trading and military location in the middle of the Pacific Ocean. By the late 19th century, as U.S. naval power increased, Hawai‘i became more attractive to the expansionist nation. American business and government interests incrementally seized control of Hawai‘i, which impacted every level of governmental control, including public health.

300–500 AD	Polynesians first inhabit Hawaiian Islands	1859	Queen’s Hospital, named for Queen Emma, is founded to provide medical care to the Hawaiian people
1778	British explorer Captain James Cook lands in Hawai‘i; he publishes an account of the “Sandwich Islands,” providing the earliest documentation of European contact with the islands	1866	Leprosy patients are first sent to Kalawao, Moloka‘i
1785	The first trading ship lands in Hawai‘i on its way to China; sandalwood trade and whaling soon become major industries	1870	Scarlet fever kills “great numbers” of Hawaiians
1804	“Okuu” (probably cholera) epidemic kills nearly 15,000	1872	King Kamehameha V dies without an heir, ending the House of Kamehameha
1810	Kamehameha formally establishes Kingdom of Hawai‘i and proclaims himself king after a 15-year struggle with the <i>ali‘i</i> (chiefs)	1874	Riots during the subsequent succession crisis are suppressed by U.S. and British troops; Kalākaua becomes King of Hawai‘i
1819	King Kamehameha II abolishes the <i>kapu</i> —the traditional religious and legal system that governed all aspects of Hawaiian life	1875	The Reciprocity Treaty signed between the United States and Kingdom of Hawai‘i provides for duty-free import of Hawaiian agricultural products into the United States and of U.S. agricultural products and manufactured goods into Hawai‘i; the growth and consolidation of sugarcane plantations and processing plants soon follows
1820	The first Protestant missionaries arrive from the United States	1884	The Reciprocity Convention extends the Reciprocity Treaty (1875) and provides the United States exclusive rights to Pearl Harbor
1828	The <i>Aedes</i> mosquito is first identified in Hawai‘i	1887	King Kalākaua is forced to sign a new constitution (the “Bayonet Constitution”) that strips the monarchy of power and severely restricts voting rights. The constitution was written by the Hawaiian League, a group of mostly Hawaiian-born American and British businessmen and lawyers who favor annexation by the United States
1835	The first commercially successful sugar plantation is opened by Ladd and Company	1888	Whooping cough kills 104
~1840	Leprosy is first diagnosed in Hawai‘i	1890	Diphtheria kills 104
1845–49	Influenza, dysentery, measles, and whooping cough kill approximately 10,000	1891	King Kalākaua dies and is succeeded by his sister, Queen Lili‘uokalani, who refuses to recognize the Bayonet Constitution and calls for a replacement
1848	King Kamehameha III enacts the <i>Mahele</i> , a land division act that introduces legal provisions for private ownership of land, opening the way for rapid growth of sugar plantations		
1853–54	A smallpox epidemic kills approximately 10,000; smallpox vaccination is made mandatory		

*Background image: Kaumakapili Church before the fire
Hawai‘i State Archives*

- 1893** The U.S. Marines arrive in Hawai'i at the request of the Hawaiian League, effectively blocking Queen Lili'uokalani from continuing her rule; the Provisional Government of Hawai'i is formed; although the U.S. Congress, in 1894, found no party guilty of a coup against the kingdom, a joint Apology Resolution of Congress nearly a century later (1993) accepted U.S. responsibility for overthrowing the sovereign kingdom
- 1894** The Republic of Hawai'i is established
- 1897** Government-led food inspection begins; Chinese Hospital opens
- 1898** The Spanish-American War begins (April 25); the U.S. Territory of Hawai'i is created when the United States annexes the islands (July 7); Pearl Harbor emerges as a key naval base for the war
- 1899** Bubonic plague kills 61; first sewers are laid
- 1918–20** Influenza pandemic kills 2,338
- 1936** Measles outbreak kills 205
- 1941** The United States enters the Second World War after the attack on Pearl Harbor (December 7)
- 1954** Democrats take control of the Territorial Legislature and push for statehood
- 1959** Hawai'i becomes the 50th state of the United States



Plague Doctor, physician wearing a 17th century plague preventive costume
Wellcome Library

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- ¹³ Jerrold M. Michael, "The 1899–1900 Plague Epidemic in Hawaii, USA," *Asia Pacific Journal of Public Health* 26, no. 1: 10.
- ¹⁴ Mohr 79.
- ¹⁵ Mohr 80.
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- ¹⁷ The first Kaumakapili Church, constructed of adobe with a thatched roof, was dedicated on August 29, 1839. In 1881 the church was torn down so that a more permanent church could be built. The new church was built in the gothic style and constructed of wood-frame and brick. It was dedicated on June 10, 1888. "History of Kaumakapili Church," Kaumakapili Church, accessed May 5, 2020, <http://www.kaumakapili.org/about-us/history.html>.
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AAI Oral History Project: An Interview with Dr. Barry Bloom



The AAI Oral History Project, which debuted in 2013, is a major initiative to provide contemporary investigators and the public a rare view into the lives and times of influential immunologists. Beginning in the spring of 2012, AAI arranged for award-winning oral historian Brien Williams, Ph.D., to undertake a series of interviews with past AAI presidents. Interviewees were asked about their family backgrounds, early interest in science, reasons for studying immunology, career and research highlights, challenges in balancing professional and private lives, and hobbies outside of the laboratory, along with major changes in immunology over the course of their careers and the future of immunology and science in the United States.

Since its launch, the Oral History Project has accumulated 48 interviews with preeminent immunologists. Please visit www.aai.org/OHP to view interviews in their entirety as well as selected clips.

Presented below are excerpts from one of the AAI Oral History Project's most recent interviews, with AAI Distinguished Fellow Barry R. Bloom (AAI '67, president 1985–86). Dr. Bloom is the Joan L. and Julius H. Jacobson Research Professor of Public Health at the Harvard T.H. Chan School of Public Health. Recognized as a leader in global health, Bloom pursues research primarily focused on leprosy and tuberculosis (TB).

This interview was conducted on May 10, 2019, at IMMUNOLOGY2019™ in San Diego. Please note that this interview has been condensed and lightly edited for clarity. To learn more about Dr. Bloom, including his year spent working in the Jimmy Carter White House, view the full interview at www.aai.org/OHP.

Discovering A Passion and Purpose

My background is pretty much undistinguished other than the fact that everybody in my family, all my uncles and one aunt, were physicians, so it was expected from the day I was born that I was going to be a doctor.... In a bolt of adolescent rebellion, I decided not to go to medical school, although I had applied and was admitted, and Rockefeller University had started a new immunology program as a graduate university, and this is what I wanted to do. One of the attractions was... one introductory course, which was one Nobel laureate after another talking about theoretical physics, quantum physics, everything you could think of, much of which we didn't understand, but we were impressed by the personalities.

Postdoctoral Training Across the Pond

My thesis was published essentially intact in an annual review called *Progress in Allergy* with, I think, 600 references. Otherwise, I think I would be driving a taxi with no paper and not much to show.

But because of a connection in the laboratory of a prior immunologist who studied in London, I decided I would study—since I had not gotten very far with cell-mediated immunity—I would study antibodies, and I went to work with professor Rodney R. Porter (AAI '73) at St. Mary's Medical School in London. Porter, as you know, won the Nobel Prize for the structure of antibodies, absolutely marvelous guy from Lancashire, very difficult to understand his dialect, but

one of the nicest and most generous and intuitively bright individuals I've ever met.

My project was very straightforward. [Porter had] learned that antibodies had two chains. My project was to find out which chain had the active site. I worked really hard, and I worked day and night, and I made my own DEAE [Diethylaminoethyl] columns, because in England at that time, you didn't buy kits or columns; you made them. So I learned a lot about how to do science, and to make a long story short, I did not find where the active site of antibodies was. [It was] another total failure. It turns out you need both chains to have an active site. I learned a lot about how to separate chains, and I had a lot of negative results.



....I got started in the business of cell-mediated immunity, a long series of failures, and for reasons not clear, I somehow lucked out at the end.

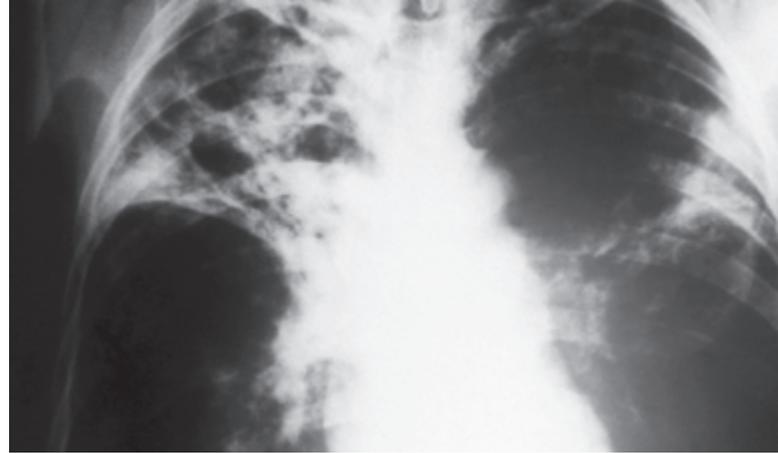
Embarking on an Academic Career

I had to return and get a job and I didn't get a huge number of offers, and, for a variety of reasons, wanted to move to New York. My wife was then a student in Asian Studies at Columbia University, so [we] returned to New York, and the original job offer was in the neurology department, because they wouldn't hire me in microbiology as I didn't have any papers. But I had an idea of what I wanted to do.... There's lymphocytes—in those days, we didn't have T cells—and there were macrophages, and the question that was raging was which cell had specificity for antigen.

My colleague Boyce Bennett spent hours with me working on how to separate cells, and what we showed is that it was lymphocytes, not macrophages, that had the specificity for antigen.

And when we showed that it was the lymphocytes that were inhibiting macrophages, and we showed that as few as a half percent of immune lymphocytes would inhibit the migration of the remainder of normal macrophages, we figured out they must be making something and secreting it... We called it migration inhibitory factor, and that was really the first of the lymphokines that had been discovered and the first non-antibody product of lymphocytes that had been described in the literature.

So that's how I got started in the business of cell-mediated immunity, a long series of failures, and for reasons not clear, I somehow lucked out at the end.



Anteroposterior (AP) x-ray of a patient's chest with advanced TB
CDC

Introduction to Global Health

The result of the paper on the lymphokines' migration inhibitory factor led to a totally unexpected invitation.... After we published the *Science* paper on cytokines and which cell had specificity for antigens,¹ I got an invitation from the World Health Organization (WHO) to come to Geneva to explain my work.

Later, WHO officials arranged a meeting in New Delhi for the following year, and there were three outsiders. One had discovered a colony-stimulating factor, which has had a great power in medicine and in the pharmaceutical industry; one discovered that there was a relationship between sickle cell and malaria; and I was the third of that group. Also there were a series of Indian leprologists, and it was all overseen by a young Norwegian named Tore Godal, who later became head of the Special Programme on Tropical Diseases at WHO and the first director of Gavi [Global Alliance for Vaccines and Immunization]. It was an extraordinary meeting. It was like a clash of two cultures.

Leprosy and TB

We knew nothing about leprosy and leprologists knew nothing about basic immunology, and the number of questions we could ask was extraordinary. [And these questions] would be easier to answer in leprosy than almost any other condition, because in contrast to TB, as you know, leprosy is caused by a relative of the tubercle bacillus called *Mycobacterium leprae*. We can't study easily what goes on in the human lung. It's very difficult. But leprosy's a skin disease. It rarely disseminates internally, probably because it doesn't grow at high temperatures, and skin is at a lower temperature, about 32 to 34 degrees centigrade.

The second striking thing about this odd disease is that it isn't a single clinical entity; it's a spectrum that correlates perfectly with the immunology. At one end of the spectrum, lepromatous leprosy, the bugs flourish. They grow essentially only in macrophages or Schwann cells around the nerves and they cause nerve damage. At the other end of the pole, there's a massive infiltration of what we would now see as CD4, CD8, and macrophages, and almost no visible bacilli. The macrophages kill off the bacilli, but in the process, they damage the nerves as well. As a consequence, it was an

extraordinary, unique opportunity to study the whole range of cellular immune responses from unresponsiveness to too much responsiveness in the context of a human disease. So I have spent a good part of the rest of my life studying immune responses in leprosy, and it has remained, at least for me, a rewarding subject.

The other extraordinary fascination about leprosy is that there's no other disease [for which] people in the Middle Ages were buried alive, burned at the stake, or thrown out of cities with a bell and candle and left to survive in the deserts on their own. It not only has a history but it has a stigma, and that led me to believe that, yes, I wanted to do basic science, but not just to write papers in *Science*, *Cell*, and *Nature*; I wanted to do basic science on real diseases with real pathogens, and at the time I started, nobody, or virtually nobody, worked on real antigens.

This was the era of reductionist science, people working on model systems, so the major antigen was dinitrophenylated bovine serum albumin [DNP-BSA]. [We were] not aware of anybody dying of bovine serum albumin as a major cause of illness, and here we were working on leprosy bacilli in patients and in animal models, particularly interested in the part of the spectrum where the immune response killed off the bugs but caused tissue damage. That struck me as very odd, and if you think of what tuberculosis is like, it's a massive immune response to wall off the bacilli that causes a hole in the lung and massive tissue damage in the lung. And while we couldn't get access to lungs, the principles, I thought, were likely to be very similar.

The other possibility was that the tissue damage we saw in skin in leprosy might be relevant to autoimmune diseases, and the particular case of interest was the possibility it might be related to multiple sclerosis, where there was infiltration of white cells into the brain with concomitant damage of nerve cells.

So I flew back from India full of enthusiasm, worked with a terrific neuropathologist at Einstein named Henry Wisniewski, and we did a really simple experiment. We

sensitized guinea pigs to tuberculin and then we injected a little tuberculin into the head of some guinea pigs to see what would happen, and what would happen was astonishing: a massive cellular response, a dissociation of the sutures that hold the brain together, and the guinea pigs' heads blew up. So we had created an artificial neurologic autoimmune disease by creating a specific immune response to a foreign antigen in the vicinity of nerve cells in the brain, and the specific response to the tuberculin led to a nonspecific damage of the nerve cells. That's what goes on in tuberculoid leprosy, and, to some extent, that may also go on in some autoimmune diseases elsewhere in the body, and that was called "bystander demyelination."

Collaborations

From there, I've worked for a large part of my career in collaboration with wonderful students and fellows. The first that I would mention on this occasion is one of my early postdocs, JoAnne Flynn (AAI '96, president 2018–19), who came with a background in microbiology and is now [2019], I'm proud to say, president of the American Association of Immunologists.

As JoAnne came to the lab, she was really good at microbiology and genetics and really didn't know anything much about immunology, so we gave her some immunology projects that turned out to be absolutely transformative for the field. It was at that time that knockout mice became available, and so we got mice that had knockouts in gamma interferon, and they died from TB very rapidly, at 21 days. We had mice that lacked tumor necrosis factor [(TNF)] and we assumed those mice would not show pathology, but, in fact, they died at the same time as the gamma interferon knockouts. We reconstructed the mice to show that if you triggered both, you need both interferon gamma and TNF to get a protective response in the mice.

JoAnne then asked, what about killer cells? And she used mice with knocked out MHC Class I and showed that CD8 and cytotoxic cells seemed to be important for protection. JoAnne really laid the basis for the fundamental cellular mechanisms of protection, in cellular terms, of how you get protection against leprosy and how you get protection against TB. We still don't know in molecular terms, any more than I did when I was a graduate student, about what molecules are really crucial for assuring protection and being necessary to develop rationally a perfect vaccine.

But to continue my studies in leprosy, [Robert Modlin (AAI '86) and I] found that there was a mechanism in humans, at least for killing TB in vitro, that depending on products of activated lymphocytes, probably interferon gamma, and other cytokines, and it worked by a mechanism totally different than what we found in mice. So in my lab, John Chan (AAI '06) and some other students and postdocs showed the major mechanism for killing TB in mice was not oxygen radicals, which is what killed most other bugs at the time, in terms of our knowledge, but it was killed in mice by reactive nitrogen oxides and reactive nitrogen species.



The...extraordinary fascination about leprosy is that there's no other disease [for which] people in the Middle Ages were buried alive, burned at the stake, or thrown out of cities with a bell and candle and left to survive in the deserts on their own.

We showed that human macrophage is killed by a different mechanism, in vitro at least, and the mechanism required the engagement of vitamin D. We worked out a completely unique pathway where vitamin D led to the production not of radicals but of a protease or an antimicrobial compound that had the ability to put a hole in the membrane of the very tough membranes of *Mycobacterium tuberculosis* and *leprae*.

To make a very long story short, we've worked out a lot of the mechanisms important for activating macrophages, at least in vitro, to control and kill TB, and we also showed that one of the things that the lymphocytes of the old days—now, CD8 T cells—did is a subset of them could not only kill infected macrophages, they could kill the TB within the macrophages. With the help of a young junior faculty named Sam Balin and Robert Modlin's lab at UCLA, we showed that this requires a subset of killer cells that is able to put a hole in the membrane of the target cell with perforin and deliver antimicrobicidal compounds granzyme and granulysin.

The Importance of the WHO

When I was invited in 1968, I think, to go to India for the first time, it's an experience I really never got over, and I was absolutely motivated to try to use science in some way, not to make drugs and vaccines in my lab, but [to] understand the basic science that might allow others to do that [and] target it on diseases of the Third World. As a result of that, this wonderful Norwegian who had created the first leprosy center in Africa....was invited to return to WHO and set up a program on leprosy, and he asked me then to join him as an advisor to that program that was called IMMLEP [Steering Committee on the Immunology of Leprosy]. It was funded, tiny amounts of money, by the Norwegian government, and my role was to try to get some of the best scientists in the world to come for nothing to WHO and share their ideas and share something else as well.

It turns out the leprosy bacillus was discovered seven years before Robert Koch discovered the tubercle bacillus. It has never been able to be grown in a test tube. It is a completely genetically degenerate organism. It barely can survive in vivo.



I was absolutely motivated to try to use science in some way, not to make drugs and vaccines in my lab, but to understand the basic science that might allow others to do that and target it on diseases of the Third World.

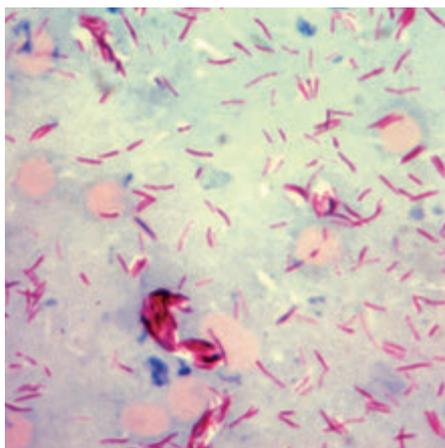
It's amazing that it actually causes a disease. Nonetheless, how do you study leprosy if you can't study the bug? It doesn't grow. Except there was a wonderful guy at CDC [Centers for Disease Control and Prevention] named Charles C. Shepard (AAI '51) with another group who showed that it did grow in two animals.

It grew in the footpad of mice, which has low body temperature, but you can't get a lot of bacilli out of a footpad in a mouse to study the bug worldwide. It also grew in a weird animal called the nine-banded armadillo, *Dasypus novemcinctus*, and these are all over the southeast of the United States. They have really crappy immune systems. Because they're encased with an armor coating, they don't need much of an immune system, and I believe that that's the major reason *M. leprae* grows. They have a low body temperature and they have a lousy immune system.

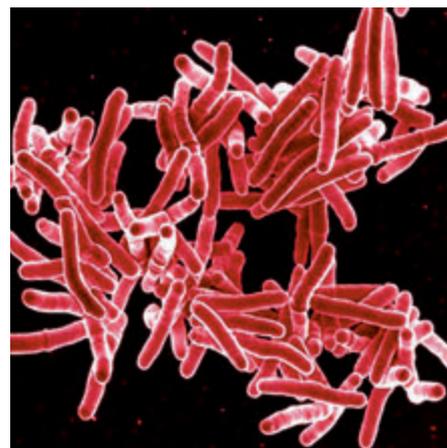
A contract was let by WHO and enabled two major laboratories studying leprosy to grow enough bacilli in armadillo livers—you could get 10^{10} per gram of tissue. That's a lot of bacilli. WHO organized that, the IMMLEP Committee oversaw that, and the bacilli that were obtained were made available at no cost to any scientist in the world qualified to study leprosy. While with many other infectious diseases, we're worried about giving anything away because they



Nine-banded armadillo
CDC



Mycobacterium leprae bacteria
CDC



Scanning electron microscopic image of
Mycobacterium tuberculosis
CDC

were interested in setting up companies, we were pretty sure there was not going to be a lot of money to be made from a company that worked on leprosy. My lab and another lab elsewhere simultaneously made the first monoclonal antibodies against antigens of *M. leprae* and *M. tuberculosis*. We gave that to WHO, and that was distributed free of charge to everybody that wanted it in the world.

Then I was privileged to meet at WHO with two giants in the field of molecular genetics, Ron [Ronald W.] Davis at Stanford and Rick [Richard A.] Young at MIT, who had invented the first really useful gene expression system, where you could clone genes into a phage lambda gt10 or gt11 and make foreign proteins from almost anything in *E. coli*, and thus we had the ability to manufacture or at least allow laboratories to make buckets of any TB or *M. leprae* antigen. And in the course of it, the DNA enabled the sequence of *M. leprae* and *M. tuberculosis* to be done. None of this would have gotten done had not a wonderful collection of people outside the field of immunology, outside the field of genetics, been willing to work for WHO for a common purpose to use their skills and knowledge and to make everything that we discovered free and open to anybody in the world.

So I became heavily involved then in WHO activities. I was the first chair of the outside advisory committee called STAC, Scientific and Technical Advisory Committee, to the leprosy program....Since it was such a model program that did the science and gave it all away, that led to the origins of the so-called Tropical Disease Research Programme [ed. Special Programme for Research and Training in Tropical Diseases (TDR)], which WHO then created for diseases like malaria, leishmaniasis, filariasis, and the hope was that they would also pull scientists from all sorts of fields together to move forward on these now-called neglected tropical diseases. So that has been an extraordinary and wonderful experience.

Then I switched. They created a vaccine program and supported research, and I chaired the committee called IMMTUB, the Immunology of Tuberculosis, and that has spurred on efforts to develop the basic science underlying

vaccines. In the last year, we've seen two papers in *The New England Journal [of Medicine]* that indicate there are now hopes for having better ways to immunize people than we've had for the last 100 years. So immunology is really making an impact on two almost totally refractory diseases. TB is now the largest cause of death in the world from any infectious disease, exceeding HIV and malaria for the first time, so this is

a serious effort that WHO has inspired and now many labs are contributing to.

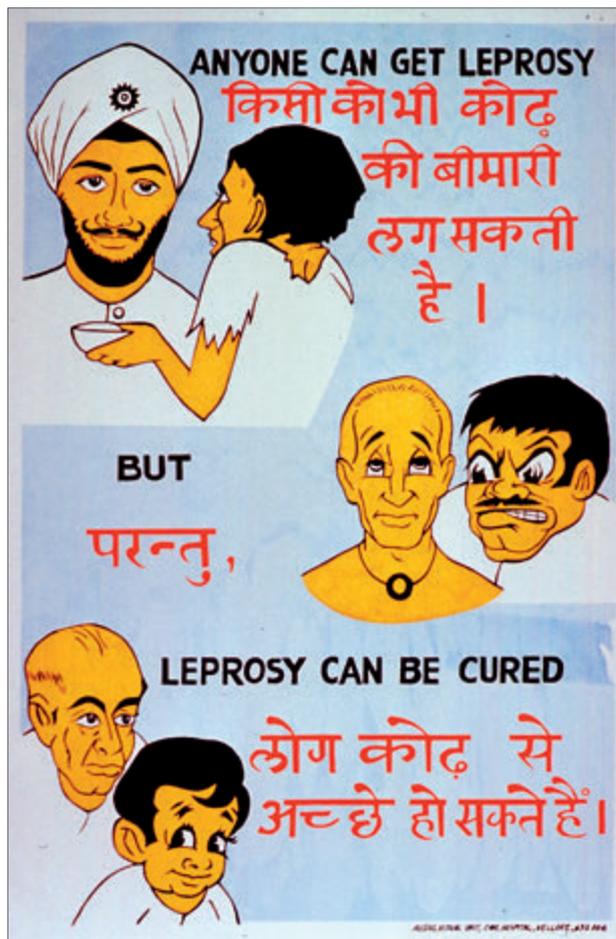
People forget that essentially all vaccines are iterative processes. The first go is never the perfect vaccine, and there is a history of almost all vaccines requiring continuous improvement. So I'm not confident that these two papers are the last word, but if they show in larger studies the kind of protection, 50 percent, or for people under 25 years of age—one of them showed 84-percent protection—when you're getting 10.7 million new cases a year, I'll take a 50-percent effective vaccine any day. It would be a *huge* impact.

Leprosy Today

So the status of leprosy is that there was a counterpart committee to IMMLEP, which was called TLEP, the mission of which was to develop drugs, and they developed drugs, tested them in mouse models. The situation with leprosy is both interesting and somewhat discouraging. It is interesting because that treatment has

been applied to those countries that have a leprosy problem. When I started, there were 12.5 million registered—leprosy is a notifiable disease to all governments. There were 12.5 million patients registered to have leprosy. Assuming that was 50 percent of all the patients, that half were missed, not least because of the stigma and their reluctance to come on, there must have been 25 million at the start of those IMMLEP and TLEP programs. There are now fewer than 800,000 registered new patients, an astonishingly effective impact of drugs, mostly on people who already had the disease. It's a very, very slow disease.

The discouraging part is the incidence rates. The number of new cases has not fallen, and what that means is people are transmitting leprosy before they know they have it and go in



"Anyone can get leprosy, but leprosy can be cured," public health poster, India

National Library of Medicine

for treatment. If they do go in for treatment, they get cured, 90-some percent cures, not a problem.

What's really important there is the only way we have to test a vaccine is very expensive long-term trials in patients at risk for TB, which is a low percentage, even in high-burden areas. What we really need to know is what are the immunologic correlates that guarantee protection. We know for polio if you have neutralizing antibody, you're protected. Done. For hepatitis B, it's exactly the same, and we even know what isotype of antibody guarantees protection. We haven't got a clue what are the essential ingredients to guarantee if you saw these cytokines, these T cells, these NK cells, and innate immune cells, this vaccine worked, this patient is protected. So we have lots of immunology yet to do.

Science and the Public

I look at my role as, in many of these aspects, [one] of making mischief, and so the current cause of mischief with which I am engaged has to do with the issue of outbreaks of vaccine-preventable diseases in the U.S. As an immunologist, you can't ignore the fact that we have now more measles cases than we've had in the last 20 years. We have a great vaccine for measles, mumps, and German measles. How is that possible in America? What does it mean to have religious and moral objections to a bloody vaccine that saves lives, and what are we going to do about it?

So in this effort, I can just say that in two editorials, one in *The Washington Post* recently and one in *The Journal of the American Medical Association* hooking up with a major educator, Scott Ratzan, and Larry Gostin, who's head of Health Law at Georgetown, we've put together a set of proposals of how we can tighten up the immunization in this country particularly, to cut out the efforts, quite successful at this point, of the anti-vaccine groups by trying to get the truth about safety and efficacy of vaccines and protect our kids who don't get a vote on this. Kids don't vote on whether they're going to be protected against measles or blindness or deafness or encephalitis or pneumonia; their parents do. And as a result, we've got to get more persuasive in protecting those kids with the tools we have.



I look at my role as...making mischief, and so the current cause of mischief with which I am engaged has to do with the issue of outbreaks of vaccine-preventable diseases in the U.S.



Barry R. Bloom, AAI OHP interview, 2019
AAI

So that's the effort that I'm engaged in, and have been quite pleased in the last couple weeks. A whole slew of vaccine experts, which I don't pretend to be, and health law experts and people administrating health programs in universities have started to join and say, "We have to be able to do something to increase the level of awareness and understanding, deal with the social media, with misinformation. Vaccines don't cause autism. Vaccines do save lives." That seems to be a battle to take on the politicians right now in—there are only two states that have not had [measles] outbreaks, and they're the states you wouldn't guess—Mississippi and West Virginia—who do not have exemptions, other than medical exemptions, for vaccines, and they have had no recent outbreaks. So it's telling you something, and we have to begin to deal with that at a legislative level in states to protect our kids.

The Diverse and Exciting Field of Immunology

Where can you get a field where you can study fundamental immune responses, regulation of a really complicated system? The dean at Albert Einstein when I was there was a neuroanatomist, and he liked to say to students, who always roared at this, that the brain is the second-most important organ of the body, and he never specified what the other organ was. For me, it was always the immune system and lymphoid system, even more complicated, probably, than the brain. The ability to recognize almost any compound, any chemical in the environment that it's never seen before and make a response to it, that's *astounding*. And then to be able to go from very basic mechanisms, from DNA and RNA and all that, to how do you develop a vaccine or a diagnostic that's going to make a difference in the world, I mean, [in] how many fields can one investigator have the freedom to find their niche in any part of a giant scientific spectrum? So it remains even more exciting now than it was when I was a student.

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HISTORY

ACUTE
ANTERIOR

POLIOMYELITIS

(A COMMUNICABLE DISEASE)

Part I—Understanding and Treating a Perplexing Disease

Keep Out of this House

By Order of BOARD OF HEALTH

HEALTH OFFICER

Person removing this card without authority is liable to prosecution.

Public notice of poliomyelitis quarantine

National Library of Medicine

In the late 19th century, sporadic outbreaks of a perplexing and debilitating disease began to appear in both the United States and Europe. Most of those affected, primarily young children, would experience a fever and perhaps some pain or stiffness and then recover. But in a small percentage, the disease would progress to paralysis of legs or the diaphragm, sometimes leading to death. Poliomyelitis, or simply polio, presented medical researchers and early immunologists with special problems that grew more urgent as outbreaks became epidemics and the effects of the disease more severe. From its inception, *The Journal of Immunology (The JI)* published some of the most important research on the nature of polio, ultimately leading to the successful vaccines of the 1950s.

The Discovery of Viruses

Although polio seemed like a new plague at the dawn of the 20th century, evidence of its paralytic effects can be traced

to ancient Egypt and ancient Greece. This disease was rare and, to all appearances, random and therefore not well understood until shortly after the discovery of viruses in the late 19th century.

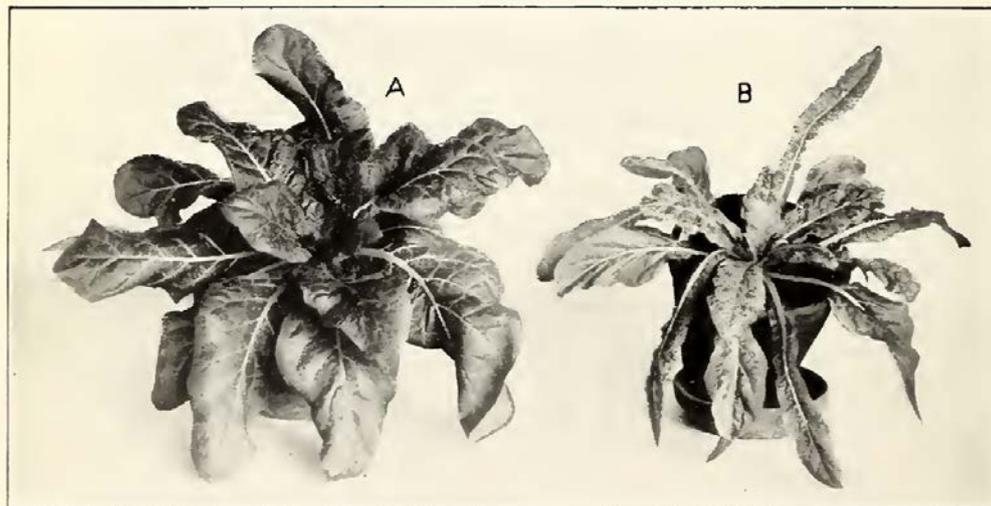


FIG. 2.—HEALTHY AND MOSAIC PLANTS OF NICOTIANA LONGIFLORA. A, HEALTHY PLANT; B, MOSAIC PLANT PRODUCED BY ARTIFICIAL INOCULATION.

Tobacco mosaic virus symptoms, 1914
U.S. Department of Agriculture

Bacteria were first seen by the naked eye with the invention of the microscope by Antonie Van Leeuwenhoek in 1668; soon thereafter the field of bacteriology was born. Virology came much later because the causative agents could not be seen even under the highest powered light microscope.

The term virus (“poison” in Latin) had been used for centuries to describe medical maladies for which the cause was mysterious. The imprecision of the

term, however, would end with the 1898 discovery of the tobacco mosaic virus (TMV), an infectious agent that could be spread through the sap of the tobacco plant.¹ The experiment underlying the discovery was rather straightforward and owed its success to the porcelain Chamberland filter, which had pores so small that a solution that passed through it would be bacteria free.

Typically, the filter was used to strain out bacteria to be tested. However, when a pasteurized aqueous solution containing crushed-up leaves of diseased tobacco plants was forced through the filter, the remaining solution could still infect tobacco plants. Though the TMV was not seen, nor could it be grown in laboratory cultures, it was the first “filterable virus” to be isolated.²

Many more viruses were soon isolated. The first vertebrate virus, foot-and-mouth, was isolated in 1898, and the first human virus, yellow fever, was isolated in 1900. And in 1935, Wendell M. Stanley (AAI 1957) was the first to crystallize a virus—the TMV—and demonstrated that it was composed of protein and ribonucleic acid. He was awarded the Nobel Prize in Chemistry in 1946 for his research.

Polio Outbreaks

In the mid-1800s, doctors were reporting clusters of infantile paralysis during the summer months in the United States and Western Europe, though the clusters were so small and sporadic that uncovering a clinical diagnosis for the disease was impossible. The first epidemic in the United States occurred in the Otter Valley of Vermont during the summer of 1894.



Charles Caverly
Rutland Herald

Charles Caverly, a diligent local doctor, was able to trace the 123 people comprising the Vermont cases and noted the sex, age, symptoms, and outcome for each. Though unable to determine the cause of the disease, he laid the groundwork by reaching three important conclusions: polio had the potential to become an epidemic; most of the victims were children, not infants, thus “infantile paralysis” was a misnomer;

and some victims experienced an extremely mild form of illness with minor symptoms and a quick recovery.³

In July 1904, the world’s first major epidemic of polio began in Sweden. The countryside around Stockholm had seen outbreaks of polio sporadically over the previous three decades, with the most recent in 1895. The 1904 epidemic began in a small village 155 miles southwest of Stockholm.

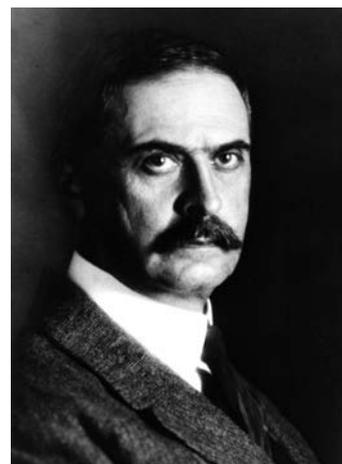
Within three months, cases had been reported in nearly every county in the country. In August alone, 360 cases were reported, and by year’s end there was a total of 1,031.⁴

A majority of the cases became the subject of a comprehensive survey by Ivar Wickman, who crisscrossed the country to get detailed accounts from victims and families. His conclusions reinforced Caverly’s hypotheses, vastly expanding the understanding of the disease: it was spread through personal contact; all infected persons, symptomatic and asymptomatic, were contagious; and the incubation period for first symptoms was three to four days after infection and a further six to eight days for paralysis.⁵

The number of polio epidemics increased in number and severity into the 20th century, and with each epidemic, understanding of the disease increased incrementally. The causative agent, however, remained a mystery.

The Polio Virus

On December 18, 1908, Karl Landsteiner (AAI 1922, president 1927–28) rose to give a talk at the Royal and Imperial Society of Physicians in Vienna. The topic of his talk was polio, and he was there to announce that he had isolated the filterable virus responsible for the disease. Landsteiner had taken a sample from the inflamed spinal cord of a child recently claimed by the disease, ground it up in sterile water, and injected it into guinea pigs, rabbits, and mice to no avail. Then he injected samples into the abdomen of two monkeys. The first died after eight days, and the second became paralyzed from the waist down before dying on Day 18 post-infection. The spinal cords of both monkeys exhibited the telltale lesions of polio. Further research using filtrates yielded identical results. The polio virus had been isolated.⁶



Karl Landsteiner
National Library of Medicine

Flexner and Early Polio Research in the United States

Back in the United States, Simon Flexner (AAI 1920), the director of the recently opened Rockefeller Institute for Medical Research (RIMR) and editor-in-chief of the *Journal of Experimental Medicine*, had begun his own polio research. By 1907, the country was also experiencing an increase in outbreaks both in number and severity during the summer months. That year, New York City health officials reported 2,000 cases, and similar outbreaks were reported in Massachusetts, Minnesota, Nebraska, Ohio, Wisconsin, and Vermont.⁷



Simon Flexner
National Library of Medicine



Brooklyn, NY, 1914
New York Historical Society

Later, after successfully reproducing Landsteiner's work, Flexner began a series of experiments to determine where the virus entered the body. And like Landsteiner and many other researchers, Flexner was using a monkey model for the disease.

This choice in model had its positives and negatives. Monkeys were able to be infected by polio, though not naturally. Like today, they were expensive and difficult to buy and maintain; by contrast, at the time of Flexner's research, the origins and previous conditions of the monkeys were usually completely unknown.

Flexner's research into the entry point for the virus began with feeding his test subjects poliovirus by mouth. None got sick. Next, he introduced the virus into their sinuses by using a swab dipped in filtrates and watched as the monkeys soon became sick. Flexner reasoned, incorrectly as it turned out, that the virus entered through the nose and traveled into the central nervous system.⁸

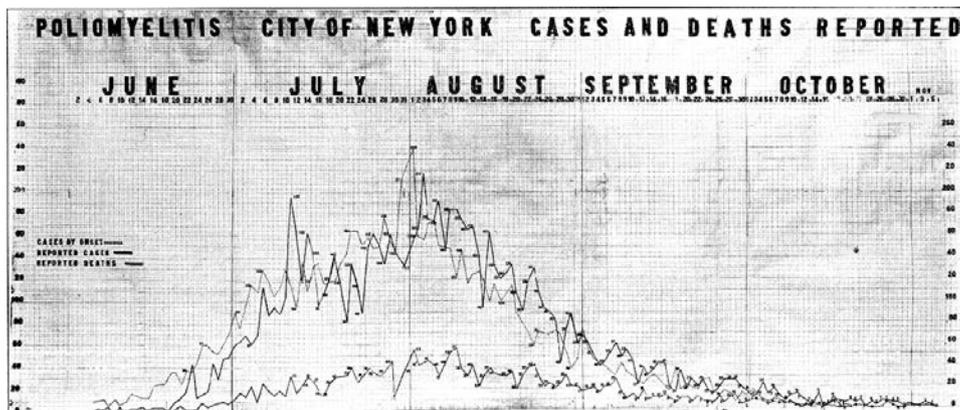
By 1911, an optimistic Flexner was quoted in the *New York Times* saying, "We have already discovered how to prevent infantile paralysis" and that the "achievement of a cure, I may conservatively say, is not now far distant."⁹

What later research would show was that, unbeknownst to Flexner, his selection of a *Macaca mulatta* (rhesus monkey) was the fatal flaw in his research because that species is unable to orally contract polio.¹⁰

The 1916 Polio Epidemic

The year 1915 proved relatively unremarkable for New York City public health officials; in terms of public health, the numbers were very similar to those in 1914. While deaths brought on by the prevailing endemic communicable diseases remained relatively constant in 1915, the maladies remained a daily threat to the nearly five million residents of the city. The top pathogen-related deaths included pneumonia (10,692), tuberculosis (10,321), diphtheria (1,271), measles (662), influenza (394), whooping cough (395), typhoid fever (327), and scarlet fever (310). There were no vaccines or effective therapeutics for any of these, and readily available laboratory testing existed for only a few.¹¹

The biggest event in the city that year was the women's suffrage parade down Fifth Avenue on October 23. The official counts for the gathering ranged from 25,000 to 60,000 participants and at least 100,000 spectators. Polio would have caused little worry to residents of the city's five boroughs, young or old, as only 70 deaths had been attributed to the disease in the entire state.



1916 New York polio epidemic chart
New York Dept. of Health, 1917

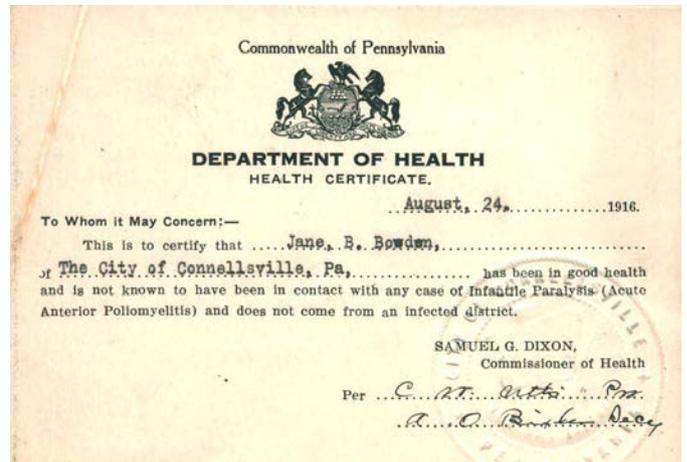
Across the United States in 1915, only 691 reported deaths were caused by polio, of which the vast majority were children under the age of five. As winter waned into the spring of 1916, there was no warning that New York City was soon to become ground zero for the first major outbreak of polio in America.

The first issue of *The JI* came out just three months before cases of polio started appearing in May of 1916 in a densely populated section of Brooklyn known as Pigtown. By year's end, the disease would claim the lives of more than 6,000 people, mostly children, and leave another 21,000 with permanent physical disability. This first major American epidemic of polio hit the New York City area hardest: about 9,000 children were affected, and 2,343 of them died.¹²

At the time, very little was known about how polio was transmitted or how to prevent infection. Because only about one percent of infected patients experience paralytic symptoms, the virus seemed less contagious than it actually was, and public health officials had difficulty identifying routes of transmission.¹³ Medical and government authorities instituted sanitation drives, food inspections, and even travel bans for children.¹⁴ Treatment options were limited during the epidemic as well. By the time polio had caused paralysis in a child, all a physician could do was prescribe medication to treat the pain and fever.¹⁵ The iron lung had not yet been developed to treat cases of respiratory paralysis.

A Catalyst for AAI Researchers

Many of the earliest AAI members would have witnessed the New York polio epidemic firsthand. Thirteen members, including Arthur F. Coca (AAI 1916, EIC 1916–1935), William H. Park (AAI 1916, president 1918–19), James W. Jobling (AAI 1914, president 1915–16), and Richard Weil (AAI 1914, president 1916–17), lived in New York City during the summer of the outbreak. Another six New Yorkers would join AAI in

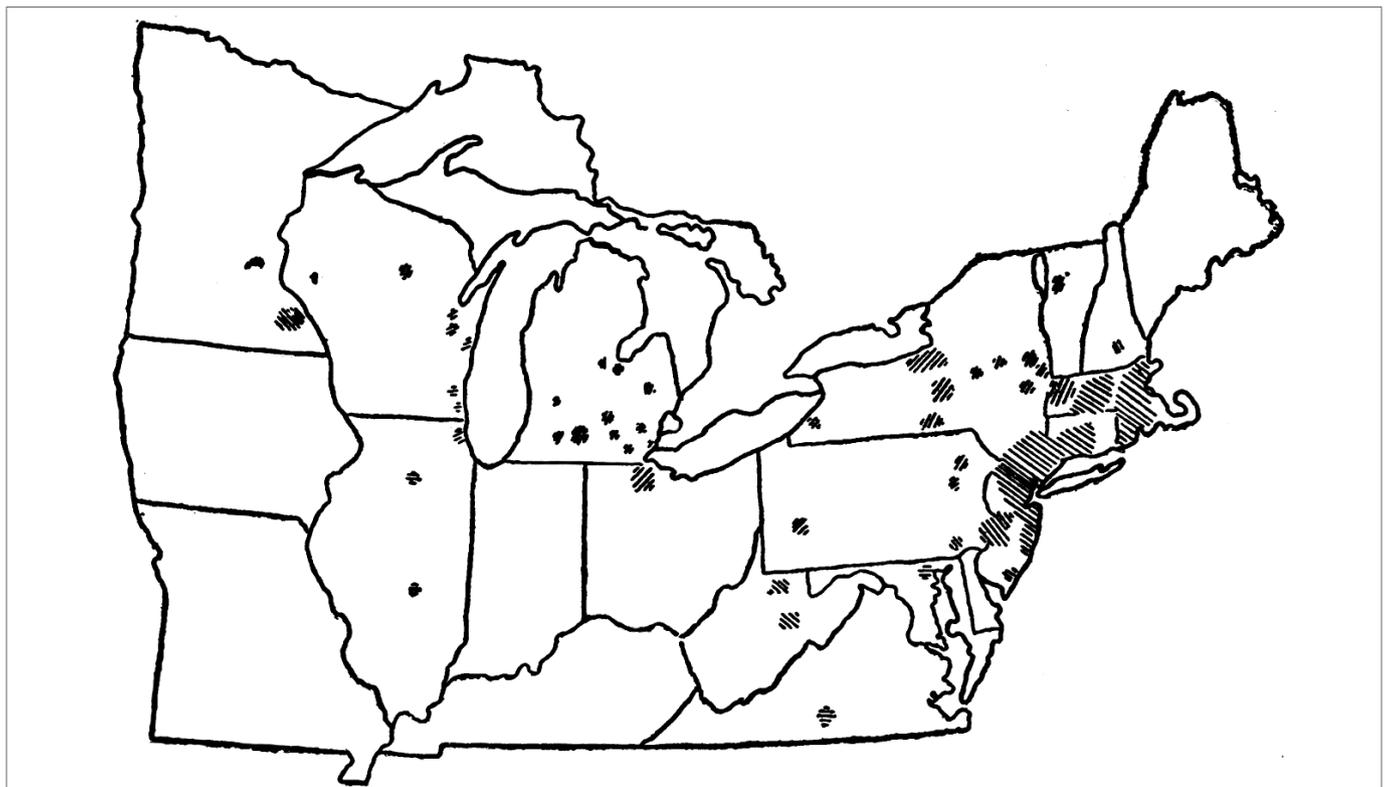


A polio health pass was required in some states due to travel restrictions, 1916
Smithsonian, National Museum of American History

the ensuing year, including Hans Zinsser (AAI 1917, president 1919–20) and Peter K. Olitsky (AAI 1917).

The 1916 epidemic inspired new research on polio, and in its early years, *The JI* published important articles that built on the previous discoveries of Landsteiner and Flexner. At this point, it was still very challenging to work with polio because the virus could not be successfully cultured in vitro. Monkeys were the only experimental animal that the virus would reliably infect, making experiments expensive as well.

John Kolmer (AAI 1913, president 1917–18) published the first article on polio in *The JI* with Anna E. Freese. Hoping



Areas particularly involved in the poliomyelitis epidemic of 1916

COMPLEMENT FIXATION IN ACUTE ANTERIOR POLIOMYELITIS¹

JOHN A. KOLMER, AND ANNA E. FREESE

From the Laboratory of the Philadelphia Hospital for Contagious Diseases

First article on polio in *The JI*

The Journal of Immunology, April 1, 1917

that a complement-fixation diagnostic could be developed for polio as had been done for syphilis, they used samples of cerebrospinal fluids and blood sera from patients in different stages of polio infection to determine (1) whether specific antigen could be detected in corresponding tissues, and (2) whether antibodies for “various and easily cultivated” bacteria could be demonstrated. Unfortunately, their research showed that the Wassermann reaction was uniformly negative for acute anterior poliomyelitis.¹⁶ They found that though there was some evidence of complement fixation with polio serum, the reactions were too insignificant to be used as a practical diagnostic.¹⁷

Seeing similarities between the polio and rabies viruses, H. L. Abramson (AAI 1918) and Herman Gerber of the New York Department of Health tried to produce a vaccine based on those analogous properties. They conducted experiments to determine if a highly potent strain of polio isolated at RIMR could be attenuated either chemically or with heat, as with rabies.

Attenuation with formalin proved “decidingly not encouraging,” so they turned to heating methods.¹⁸ Abramson and Gerber showed in monkeys that a course of five injections of the heat-treated virus over five days could produce substantial immunity to the potent virus when introduced later.

A Return to Polio Research

Polio continued to plague American children: 1921 and 1925 had significant spikes in cases and deaths, and 1927 was the worst year since 1916.¹⁹ After a gap of almost 10 years, polio research in *The JI* picked up again with wide-ranging approaches to understanding immunity to the disease. In 1927, W. Lloyd Aycock and J. R. Kagan reviewed the state of polio vaccine science and showed that it was possible to produce immunity without active symptoms.²⁰

The Kolmer and Brodie Vaccine Trials

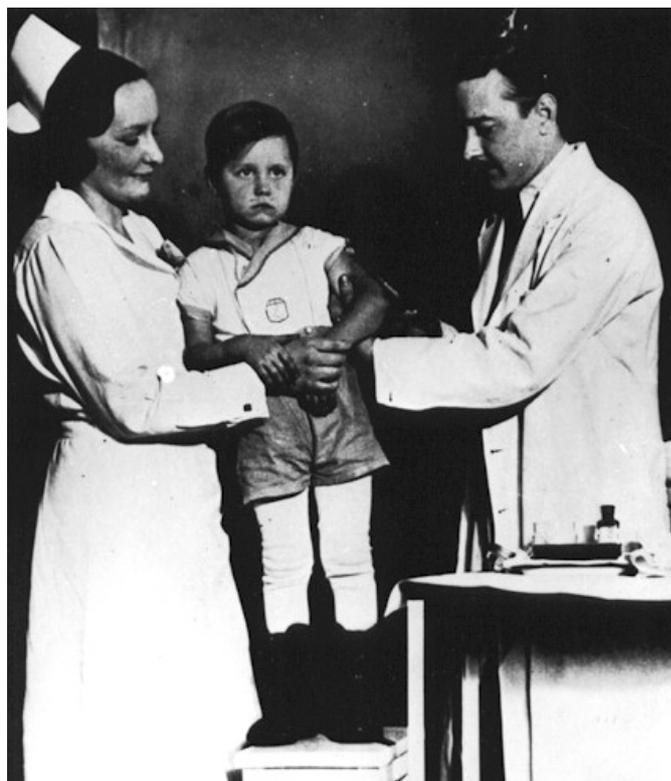
By 1934, research had advanced sufficiently to make the first serious human trials possible. As in the case of the competing Salk and Sabin vaccine efforts that would come later, two scientists independently developed initial polio vaccines, one using killed virus and one using attenuated.

John Kolmer attenuated the virus with sodium ricinoleate to produce a vaccine.²¹ Monkey tests looked promising, so

he then tested his vaccine on himself and his assistant with no ill effects. Kolmer quickly moved to tests on children. His own sons received it first, and then he distributed it to physicians across the country. In September 1935, he reported that 10,725 children had been given the vaccine, and none who had received all three doses had contracted polio. There were, however, nine cases in children who had only one or two doses.²²

Also in 1934, Maurice Brodie (AAI 1934) began work on a polio virus in the Bureau of Laboratories of the New York Department of Health under William H. Park. Using formalin-killed virus, he produced humoral immunity in monkeys reliably, but tissue immunity in only a few (a live virus had the opposite ratio). The common belief at the time was that tissue immunity was the more important component of protection from the virus.²³ Like Kolmer, Brodie swiftly moved to human trials on more than 4,500 children. He also reported five cases of polio among the vaccinated subjects, but two of those children had been exposed just prior to receiving the vaccine, and another only 13 days after getting just a single dose.²⁴

Now there were two vaccines that offered the promise of bringing an end to the scourge of polio. Sidney Kramer made a large comparative study to verify efficacy of these two vaccines, funded partly by the President's Birthday Ball Commission for Infantile Paralysis Research, the original precursor to the March of Dimes.²⁵ The study showed that neither vaccine was significantly more effective than a



John Kolmer injecting his son with polio vaccine, 1935
Detroit News

control. Kramer cited private correspondence in which Kolmer said that he no longer believed that sodium ricinoleate actually attenuated the virus.

At the 1935 American Public Health Association annual conference, both vaccines were denounced as ineffective or dangerous. Brodie acknowledged the failure of his work in person.²⁶ Ultimately, however, Brodie's vaccine did produce immunity in children comparable to the natural immunity of adults (75 percent), but the concerns raised in 1935 by the scientific community effectively barred further research at the time.²⁷ Much later research suggests that the cases of polio in children who received Kolmer's vaccine may have been provoked by the monkey spinal cord antigens, which

were present due to the production method of the vaccine and not from the introduced virus itself.²⁸

In the ensuing years, polio remained a significant problem in the United States, with most years seeing 4,000 to 10,000 cases. The numbers began skyrocketing in 1943, but by that time the outbreak of the Second World War had funneled research away from diseases such as polio in favor of studies addressing the immediate needs of the war.

In the next issue of the AAI Newsletter, we will pick up the story of polio as it played out in the postwar years, as growing outbreaks spread to more cities and suburbs. Our focus will be on the basic research that made effective polio vaccines possible.

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POLIO: PART II

THE BASIC RESEARCH BREAKTHROUGH



John F. Enders's Flasks of Poliovirus Cultures
National Museum of American History

In the previous issue of the AAI Newsletter, we presented the history of polio research in America up to the 1930s. See “Polio: Part I—Understanding and Treating a Perplexing Disease” in the December 2020 issue.

The rejection of the Kolmer and Brodie polio vaccines as too dangerous was a setback in terms of scientific research (see “Polio: Part I” in the December 2020 issue of the *AAI Newsletter*), but at the same time, popular sentiment was being mobilized to fight the disease. President Franklin Delano Roosevelt had contracted polio as an adult in 1921 and had found some relief through hydrotherapy in the waters of Warm Springs, Georgia. This experience inspired him to advocate for more effective treatments for what was then known widely as infantile paralysis.



President Roosevelt's Roman-themed birthday party, 1934
Franklin D. Roosevelt Library and Museum

The National Fight Against Polio

On January 30, 1934, Roosevelt's inner circle of friends celebrated his birthday at the White House dressed in Roman togas, poking fun at critics' claims that the president had dictatorial ambitions.¹ They were not the only ones commemorating Roosevelt's birthday. In cities and towns across the country, Americans danced, celebrated, and raised over \$1 million for the President's Birthday Ball to Combat Infantile Paralysis. At each of the numerous events, 70 percent of the proceeds went to local polio treatment and relief, while the remainder helped fund the Warm Springs Foundation.²

The Birthday Ball immediately became an annual event. Beginning in 1935, the President's Birthday Ball Commission for Infantile Paralysis Research mobilized to “wipe out the disease itself” on a national scale.³ Ahead of that year's Ball, Roosevelt named Paul de Kruif (AAI 1921) secretary of the Commission and tasked him with the responsibility of determining how to distribute the 30 percent of proceeds not retained for local care.⁴ They wanted a cure, not just treatment.

The March of Dimes

Three years later, Roosevelt reorganized the Commission into the National Foundation for Infantile Paralysis (NFIP). The popular comedian and singer Eddie Cantor told radio listeners to send “a march of dimes all the way to the White House,” and Americans responded by mailing in 80,000 dimes in addition to the \$1.5 million collected for the 1938 Birthday Ball.⁵ Contributions kept climbing: in 1945 the March of Dimes raised nearly \$19 million. Like donations, however, cases of polio were steadily increasing.⁶

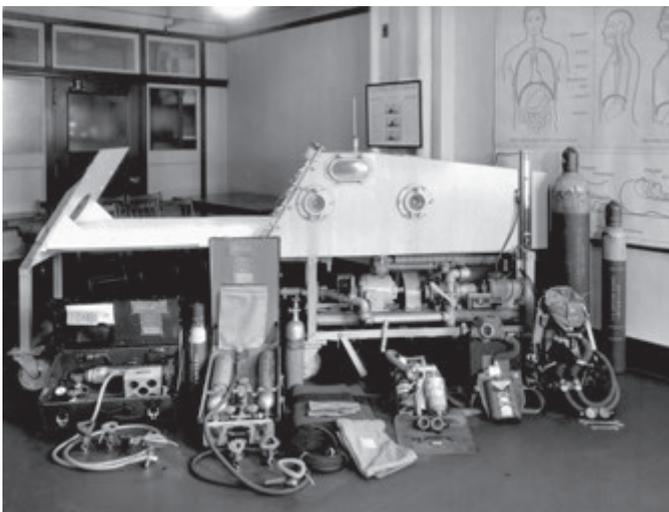
Treatment and Research

Polio was the second-most researched human virus worldwide from 1935 to 1960, only exceeded by influenza.⁷ But without a vaccine, the most effective treatment for patients suffering the most life-threatening effects was the iron lung. By enclosing the patient's torso in a chamber in which the air pressure could be increased or decreased, the device kept paralyzed lungs pumping. The iron lung was first used on a polio patient in 1928, but for the next decade the technology was extremely expensive and hard to obtain—by 1936 there were still only 222 in operation worldwide.⁸ In 1937, Edwin Both invented a much less expensive respirator that could be produced easily and rapidly. The newly available technology increased survival rates significantly but could do nothing to prevent long-term paralysis.

The War Years

When the United States entered the Second World War, research on primarily childhood diseases like polio was deprioritized in favor of diseases that would affect military readiness at training bases in the United States or fighting overseas.

In Boston, a little-known assistant professor at Harvard Medical School (HMS) was encouraged to direct his research toward mumps for the war effort.⁹ Because other more established researchers were working on the major war-related diseases, such as influenza, typhus, and yellow fever, there was little room (or funding) remaining for John F. Enders (AAI 1936, AAI president 1952–53), so he began a new study



Drinker Respirator, the first widely used iron lung, ca. 1930
Harvard Medical School Library



Poster for President's Birthday Ball, 1939
Library of Congress

on mumps.¹⁰ This seemingly small choice of switching to non-clinical, *in vitro* mumps research would yield significant discoveries about the disease and, within a decade, also break the logjam that had prevented progress in polio research.

On the home front during the war, the number of polio cases continued to climb each year, from 4,033 in 1942 to 12,449 the next year, and to 19,029—with 1,433 deaths—in 1944.¹¹

The Journal of Immunology (*The JI*) published a few articles on polio over the course of the war, most of them by S. D. Kramer at the Michigan Department of Health. Kramer had been prolific in polio research from the late 1930s, demonstrating in 1939 that the poliovirus could be found in the stools of apparently healthy carriers.¹² Supported by grants from the NFIP, Kramer was able to continue working on polio

through the war, publishing research on the production of immunity in mouse models.¹³

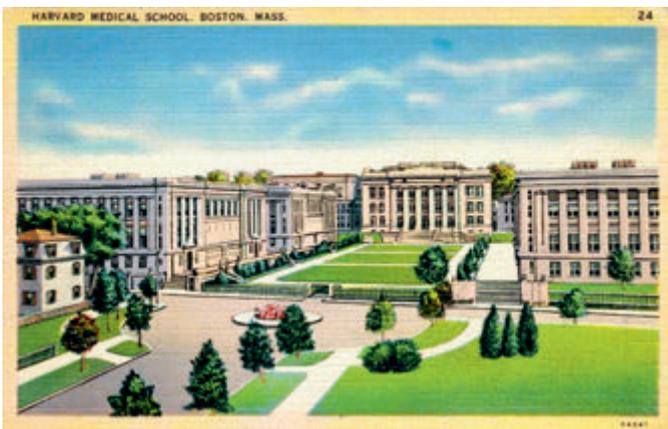
A New Understanding of Poliovirus

A dramatic rise in polio case numbers following the end of the war led to a major resurgence in polio research. Widespread use of the iron lung was saving many children from death, but also leaving increasing numbers with chronic disabilities. With the war over, researchers were free to focus on this new rising threat. Joseph L. Melnick (AAI 1948), who would later become a titan in polio research, was one of the first to publish on polio in *The JI* in peacetime. In 1946, he had been working on novel applications of the ultracentrifuge to isolate the poliovirus from monkey stool.¹⁴ The proliferation of the virus in the gastrointestinal tract inspired Melnick's later classification of the group of enteroviruses, with the poliovirus as its prototype.¹⁵

John F. Enders

All research on a polio vaccine to that point had been performed without the ability to culture the poliovirus. For any experiment on polio, the virus had to be isolated and purified from monkeys, which increased the time and cost involved in the process. It was also widely accepted that the virus would only grow in nervous tissue, which was difficult to culture and grow *in vitro*. Three researchers at HMS, led by Enders, made the key discovery that would lead to effective vaccines not only for polio but also for a range of other common viral diseases.

John F. Enders had a unique background among his peers at HMS. He was classically trained in English literature, including



Postcard of Harvard Medical School campus, ca. 1941

research in Celtic and Teutonic language, having earned an A.B. and M.A. in the field. He was working on a Ph.D. with the goal of becoming an English teacher before a chance encounter with Hans Zinsser (AAI 1917, AAI president 1919–20), professor of bacteriology and immunology at HMS.¹⁶ In 1925, Enders accompanied a friend from his boarding house, Hugh Ward, who was an instructor in Zinsser’s department, to the laboratory as he changed some media in bacteria cultures. Enders later wrote that “[Zinsser and I] soon became friends, and thus I fell into the habit of going to the laboratory with him in the evening and watching him work. I became increasingly fascinated by the subject—which manifestly gave him so much pleasure and about which he talked with such enthusiasm—and so eventually decided to change the direction of my studies.”¹⁷

Virus Research

Enders soon switched from a Ph.D. in English to one in bacteriology and immunology (which was unusual because at the time an M.D. was more common for both clinical and basic researchers in the field). He then spent the next 15 years working with Zinsser. His first faculty appointment came at the age of 32. Initially his research focused on immune responses to bacteria, but in 1937 he made the move to viruses.



Thomas Huckle Weller, 1968
National Library of Medicine

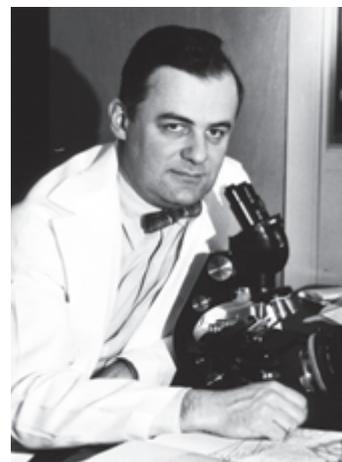
Enders began his virus research while working with William McD. Hammon (AAI 1946) on a usually fatal disease in kittens known as panleukopenia, also known as cat distemper or enteritis. Enders and Hammon identified the virus that causes the disease and demonstrated that the virus initially infects the bone marrow. They created a vaccine that quickly became the standard in veterinary care.¹⁸

Enders also began research on the growth of the herpes simplex virus, assisted by then fourth-year medical student Thomas

Weller (AAI 1943).¹⁹ Their initial work on the tissue-culture method was interrupted by the outbreak of the Second World War, when Weller left to serve as head of the Departments of Bacteriology, Virology, and Parasitology at the U.S. Army Antilles Medical Laboratory in Puerto Rico.

The New Enders Lab

In 1947, the Boston Children’s Hospital asked Enders to establish an infectious disease laboratory, which would be partially funded through a five-year basic viral research NFIP grant to HMS. Enders and Weller were soon joined by the third member of their team, Frederick C. Robbins (AAI 1952), who had been the chief of the Viral and Rickettsial Disease Section of the Fifteenth Medical General Laboratory of the U.S. Army, serving in North Africa and Italy.



Frederick C. Robbins, 1955
National Library of Medicine

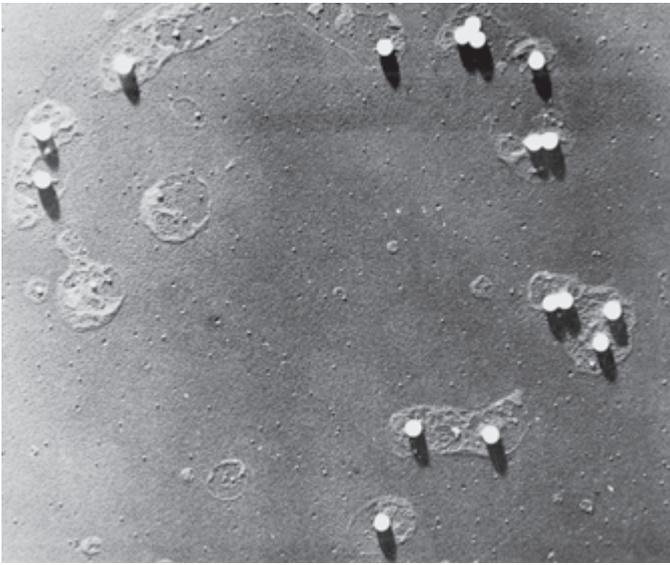
Initially, all their research was viral, but none of it was on polio. Enders continued his mumps research, while Weller went to work on chicken pox and Robbins on the viral cause of infant epidemic diarrhea. All three, however, were working on in vitro cultivation to grow their viruses.

In 1948, Enders and Weller developed the first successful method for growing the mumps virus in vitro using a culture of mainly chicken-embryo fragments and ox blood. Weller then took that method and attempted to grow the chicken pox virus in vitro with embryonic human muscle and skin as the culture, with the addition of a combination of penicillin and streptomycin to eliminate bacterial contamination.²⁰ Importantly, Weller discovered that if the nutrient media was changed at regular intervals, the tissue would live longer, thus allowing more time for the virus to propagate.²¹

The Breakthrough

Having some leftover culture flasks from his chicken pox experiment, and at Enders’s suggestion, Weller added some of the Lansing Type II poliovirus they had in the laboratory’s freezer. At the same time, Robbins was readying his cultures for experiments to identify viruses responsible for infant diarrhea using mouse intestines and used the Lansing strain in a few of his flasks. Poliovirus grew successfully in Weller’s cultures; it did not in Robbins’s.²² Weller’s successful experiment led the team to quickly refocus all their research on growing poliovirus in vitro.

To that point, polio was still considered primarily a disease of the nervous system. But the composition of Weller’s culture, combined with the abundance of recent research showing that poliovirus was found in the gastrointestinal tract of humans, inspired the three scientists to attempt to



SEM image of polio virions
CDC

culture it in non-nerve human embryonic tissue, including intestine.²³ The team successfully cultured all three strains of poliovirus, opening up the possibility of in vitro studies of the virus and enabling rapid development of effective vaccines.²⁴ Expensive monkeys—and the risks involved with maintaining a population of infected animals—were no longer necessary to produce the virus for research. Their technique also led to the isolation of several other viruses and the development of corresponding vaccines: measles, rubella, mumps, herpes simplex, and herpes zoster. Their research was published in a three-part series in the December 1, 1952, issue of *The JI*.²⁵

Nobel Prize

The trio received the Nobel Prize for “their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue” in 1954 after some controversy in the Nobel committee. Enders had first been nominated individually in 1952. Sven Gard, the chair of virology at the Karolinska Institut, had long been involved in polio research and evaluated the nomination favorably but expressed reservations about awarding the Prize to Enders alone. The next year, John Dingle (AAI 1941, AAI president 1957–58) nominated Enders along with Weller and Robbins, but the nomination was not advanced. In 1954, the Nobel Committee received nine nominations for Enders, two of which included Weller and Robbins.²⁶

This time, Gard was determined that the Nobel Prize go to the scientists who had unlocked the mystery of polio. The Nobel Committee initially recommended Vincent du Vigneaud as the laureate, but Gard enthusiastically pushed the Nobel Assembly at Karolinska Institut, the body responsible for the final decision for the Prize in Physiology or Medicine, not to follow the recommendation of the Committee and instead select Enders, Weller, and Robbins. The Assembly accepted Gard’s arguments and awarded the team the Nobel in 1954. News of the unusual behind-the-scenes dispute was leaked to the *New York Times*, but du Vigneaud received some consolation when he was given the Nobel Prize in Chemistry the very next year.²⁷

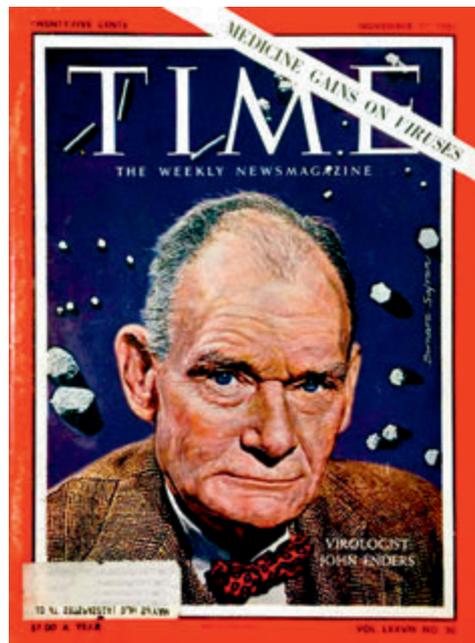
Even as Nobel Laureates, Enders, Weller, and Robbins are not familiar names like Salk or Sabin are today because their work was not as public facing as the vaccine creators’. Nevertheless, their discovery came at a crucial time when polio was affecting more children than ever before.

Toward a Vaccine

In the fall of 1949, Jonas Salk (AAI 1947), the nearly 39-year-old director of the Virus Research Laboratory at the University of Pittsburgh School of Medicine, wrote to Enders requesting a sample of a successful culture material for growing poliovirus. Salk, searching for a faster way to produce a killed virus vaccine, was deferential to Enders, stating that he did “not want to intrude on any things you might be doing or want to do...if you have already made plans to do any studies of this sort on your own.” Enders initially turned down Salk’s request as they were conducting some preliminary studies toward a vaccine.

Unbeknownst to Salk, Enders and his two younger colleagues were at odds about the next step of their research. Enders viewed vaccine research as beneath basic researchers, and a problem more suited for industry to undertake. Furthermore, he recognized that their relatively new lab was “not set up for vaccine production.” As head of the lab, Enders’s argument won the day and samples of and techniques for tissue culture were shared with Salk. The race toward a successful vaccine was gaining speed.²⁸

In the July issue of the AAI Newsletter, we will cover the application of this basic research to the development of successful polio vaccines and the legacy of the national drive to defeat an epidemic disease.

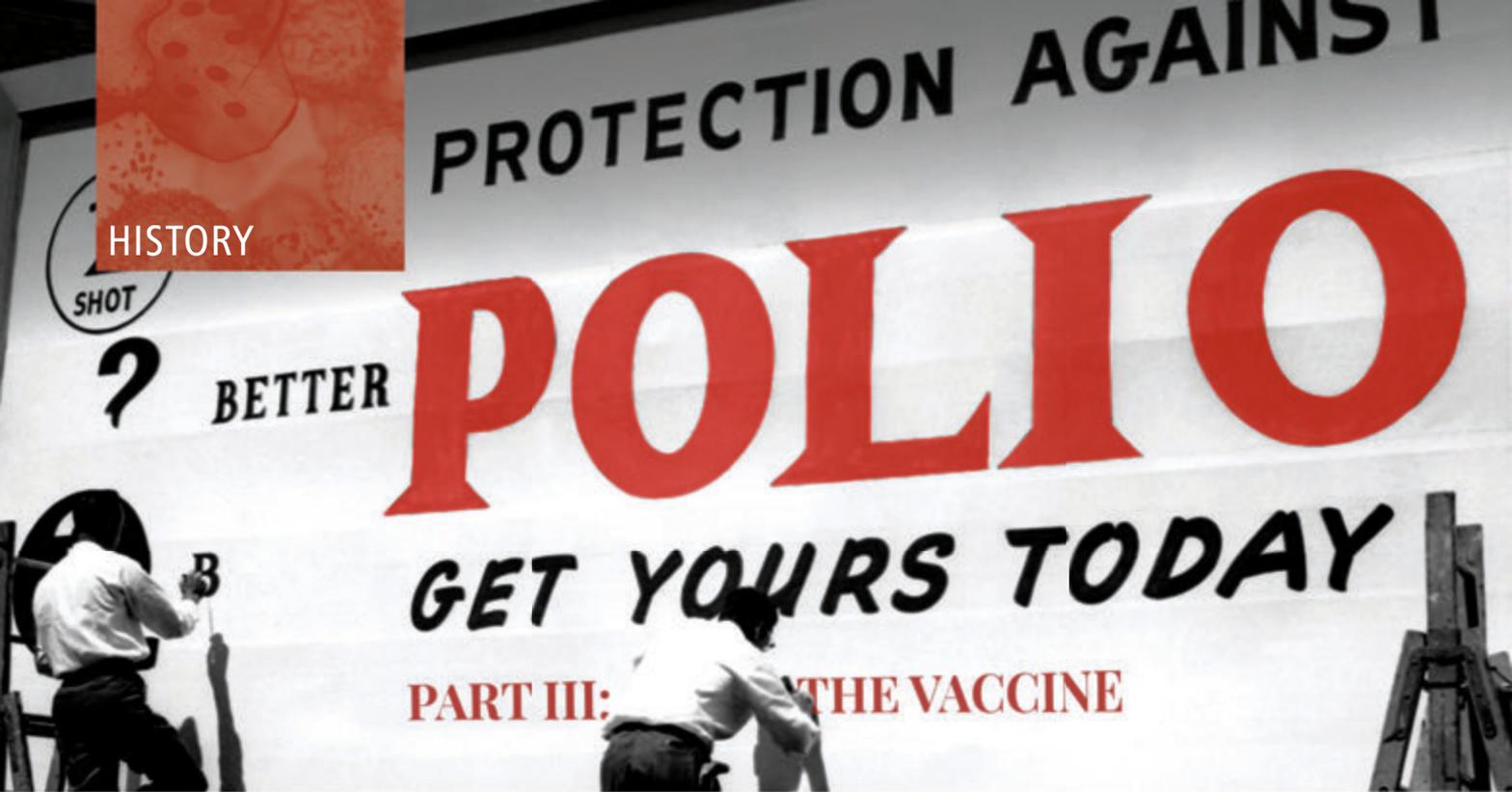


John F. Enders, cover of *Time*, Nov. 17, 1961
Time Magazine

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HISTORY



In previous issues of the AAI Newsletter, we presented the history of polio research in America from the mid-1800s through 1949. See “Polio: Part I—Understanding and Treating a Perplexing Disease” in the December 2020 issue and “Polio: Part II—The Basic Research Breakthrough” in the February 2021 issue. Here we present the final installment in the series.

Once John F. Enders (AAI 1936, AAI president from 1952–53), Thomas Weller (AAI 1952), and Frederick Robbins (AAI 1952) had successfully cultured the poliovirus, the possibility of an effective vaccine for the worsening scourge of polio was in sight. The basic science breakthrough for replicating poliovirus occurred in 1949, a year also marked by a huge surge in polio cases. Polio case rates had been increasing since 1942, but 1948 was the first year to exceed the rates of the initial major epidemic in 1916, with 28.07 cases per 100,000 Americans.¹

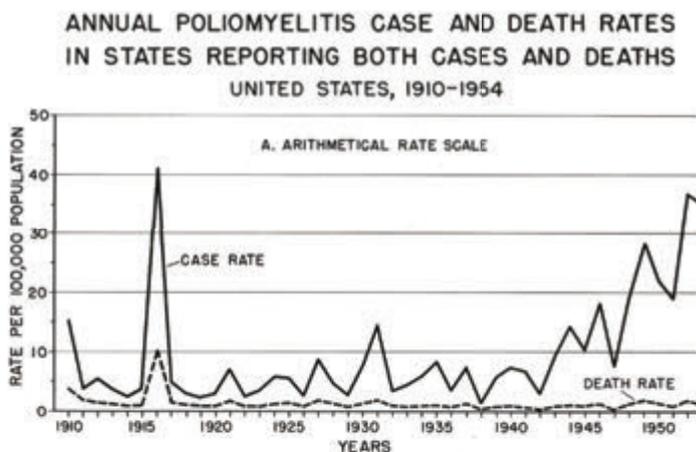
The rate increase was a reflection of the rebounding birthrate from its nadir during the Great Depression, together with the massive expansion of military service personnel after the United States entered the Second World War in December 1941.² The birthrate slowly increased from a low in 1936

through 1944; a slight lull in 1945 was followed by a “baby boom” beginning in 1946.³ Because polio was primarily a disease of the young, this increasing population of children in the United States provided the virus with more potential victims and carriers.

The need for a vaccine was as pressing as it had been during the 1916 outbreak, except this time there was a light at the end of the tunnel. Multiple researchers were actively developing new vaccines based on a clearer understanding of poliovirus.

Hilary Koprowski

On the Pearl River, New York, campus of American Cyanamid Company in 1947,⁴ Hilary Koprowski (AAI 1946) began working independently on a polio vaccine unbeknownst to



Graphs of polio cases in the United States, 1910–54
Eisenhower Presidential Library



Postcard depicting Pearl River campus of Lederle Laboratories, ca. 1955
New York Heritage

his superiors. Having previously worked with Max Theiler on his successful yellow fever vaccine, Koprowski believed he could use the same attenuation process with poliovirus. His attenuated live strain oral vaccine proved successful in preliminary animal trials, so Koprowski administered the oral vaccine to himself in 1948—and it resulted in an antibody response against the poliovirus.

In 1950, Koprowski conducted his first clinical trial on 20 disabled children in

Rockland County, New York.⁵ The trial was a success as all the children showed a positive antibody response, excreted the attenuated strain, and, in all but two cases, were not susceptible to reinfection via the attenuated virus. When the initial results became public, Koprowski was met with swift national and international condemnation about his choice of subjects (clinical consent laws were far more permissive at that time). Despite the pushback, Koprowski and American Cyanamid continued with their polio vaccine research.

Jonas Salk

Jonas Salk (AAI 1947) was born in New York City to poor Ashkenazi Jewish parents; his father was a first-generation American born in New Jersey, and his mother fled Russia to the United States when she was 12. Salk was nearly two years old when the 1916 polio epidemic gripped the city. Intermittent polio outbreaks continued in New York as Salk grew up. He completed his primary education, graduated from the City College of New York, and enrolled at New York University (NYU) College of Medicine in 1934 with the intention of becoming a researcher rather than a clinician. That same year, Thomas Francis Jr. (AAI 1930, AAI president 1949–50) isolated the influenza A virus at the Rockefeller Institute for Medical Research.

Salk became especially interested in bacteriology and problems of immunization, and toward the end of his medical training, he benefited greatly from the mentorship of Francis, who had moved to NYU College of Medicine. In 1940, Francis isolated the influenza B virus while Salk was on the staff of Mount Sinai Hospital. As Salk later described it, he “saw the opportunity...to test the question as to whether we could destroy the virus infectivity and still immunize.”⁶

In 1942, Salk followed Francis to the University of Michigan School of Public Health, where they created a killed-virus

vaccine for influenza. Three years later, the United States Army—which had been the major funder of the research—administered the vaccine to eight million soldiers, reducing their rate of infection by 92 percent in that year’s epidemic.⁷ This success would be the model for Salk’s later work on polio.

The Salk Vaccine

In 1947, seeking to gain some independence from his mentor, Salk took a position at the University of Pittsburgh School



Child getting a shot watches Jonas Salk on television inoculating child with polio vaccine, 1955
National Library of Medicine

of Medicine, where he initially continued work on influenza.⁸ Shortly after he arrived, the director of the National Foundation for Infantile Paralysis (NFIP) asked him to participate in a poliovirus typing program. That research was not especially exciting to Salk. He later said that most people looked on it as “routine drudgery,” but it gave him a comprehensive and fundamental understanding of polio at just the right moment as Enders, Weller, and Robbins were successfully cultivating the virus.

Enders and his colleagues were at odds about whether to steer their research towards creating a vaccine. Enders argued against it because he did not view vaccines as basic research, and their laboratory was ill-suited to transition to polio vaccine research. His argument prevailed and samples, data, and techniques were shared with Salk and his laboratory in Pittsburgh.

Salk, with NFIP funding, built on the work of Enders, Weller, and Robbins, and applied the techniques he had refined with influenza to develop a killed-virus vaccine for polio. The driving principle behind using inactivated virus was to streamline the testing process to get a vaccine to the public as quickly as possible.

After growing large quantities of poliovirus in a culture of monkey kidney cells, Salk, along with his small research team that included Julius Youngner (AAI 1950), Byron Bennett, and L. James Lewis, killed the virus with formaldehyde and injected this inactivated polio vaccine (IPV) into monkeys. When the tests showed that the vaccine produced immunity as evidenced by a specific antibody response, Salk moved on to humans. The clinical trials of the Salk vaccine began in 1952. All trials were overseen by Thomas M. Rivers (AAI 1921, AAI president 1933–34), a renowned virologist who was chair of the NFIP committees on research and vaccine advisory.

HISTORY

The first small trials were conducted at institutions near Pittsburgh—the D.T. Watson Home for Crippled Children and the Polk State School, established for “feeble-minded” children of western Pennsylvania—and successfully demonstrated antibody production in humans after vaccination.⁹ The following year, a pilot study with 15,000 children (including Salk’s own sons) was undertaken to optimize the vaccine schedule.¹⁰

Polio Pioneers

In 1954, the largest field trial of a vaccine in history began. Designed and led by Francis, now the director of the University of Michigan Poliomyelitis Vaccine Evaluation Center, the year-long nationwide clinical trial was conducted by over 100 researchers on nearly two million children who volunteered for the study—some receiving the vaccine, and others a placebo—at a cost of over \$17 million (more than \$169 million in 2021 dollars).

All the volunteers received a “Polio Pioneer” card certifying their participation. On April 12, 1955, the 10-year anniversary of President Franklin Roosevelt’s death, a national and international press contingent arrived at the overfilled Rackham Auditorium of the University of Michigan, where Francis declared on live television that the Salk vaccine was safe and effective.¹¹ Later that day in an interview with Edward R. Murrow, Salk told the celebrated interviewer that “there is no patent. Could you patent the sun?”

With the vaccine approved, the federal government wanted a quick rollout to prevent another epidemic as summer approached. Within hours of the vaccine’s



Cart loaded with Wyeth polio vaccine, 1963
CDC

approval, the NIH Laboratory of Biologics Control (LBC), under the authority of Secretary of Health, Education and Welfare Oveta Culp Hobby, licensed six companies to produce it: Eli Lilly, Parke-Davis, Wyeth, Sharp & Dohme, Pitman-Moore, and Cutter Laboratories.¹²

After two weeks, these companies had produced only 10 million doses, nearly all of which had been promised to the NFIP at no charge for an initial round of immunizations of first- and second-graders as well as the “Polio Pioneers” who had received the placebo, leaving the vast majority of children unprotected.¹³ The executive branch had no plan for distribution, reflecting the assumption that it was best left up to the free market. After a massive public outcry, President Dwight Eisenhower committed to “a large federal role in the distribution and financing of this vaccine.”¹⁴

Throughout the spring and summer of 1955, children around the country lined up to receive their shot at local elementary schools, a logistical marvel that involved training 60,000 medical personnel, 64,000 teachers and principals, and 220,000 volunteers.¹⁵

The Cutter Incident

Only two weeks into the initial vaccine rollout, reports of polio symptoms in a few vaccine recipients began to emerge. The surgeon general placed a pause on all vaccinations on May 8, 1955, while the cause was determined. Investigators discovered that Cutter Laboratories had released a batch of 120,000 doses of the IPV that contained *live* poliovirus.

The error’s cause was cell debris that prevented sufficient exposure of the virus to the inactivating agent. Additionally, poor oversight from the LBC allowed the active-virus doses to be distributed to and injected at vaccination sites. A third of these doses resulted in children contracting abortive poliomyelitis, a form which produces minor symptoms, because it does not involve the central nervous system, but which is still transmissible. Worse, 56 children developed the paralytic form of the disease, resulting in five deaths. Another

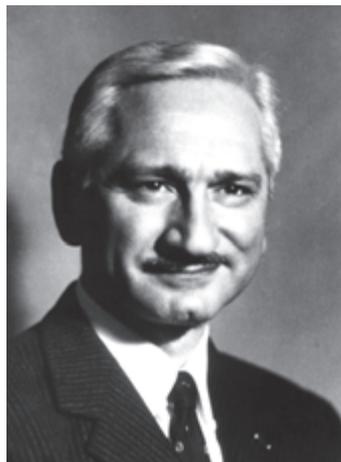


Line for polio vaccine, San Antonio, TX
CDC

five children died and 113 were paralyzed after contracting polio from one of the vaccine recipients.¹⁶

The Cutter incident was one of the worst pharmaceutical disasters of all time, but the comprehensive investigative response and increased federal safety protocols it triggered ensured that the 400 million doses of the Salk vaccine produced from 1955 to 1962 were safe and effective.¹⁷ Several of the officials involved in the original licensing and safety decisions resigned, including Secretary Hobby and NIH Director William H. Sebrell Jr.

The children and families who benefitted from successful vaccination responded with a flood of letters expressing their appreciation and relief at being freed from the horrible dread of polio.¹⁸ Looking back on the tragedy, John Enders wrote that the lesson to be learned was that “we must never again allow decisions about essentially scientific matters to be made for us by people without training or insight.”¹⁹



Albert B. Sabin, 1957
National Library of Medicine

Salk's. In 1936, working with Peter Olitsky (AAI 1917) at the Rockefeller Institute, Sabin had been successful in cultivating poliovirus in vitro in human embryonic nervous tissue, but that experiment had used a strain that had undergone 20 years of brain-to-brain passage in experimental monkeys. Thus, when the same virus failed to grow in non-nervous tissue, it appeared to confirm the common finding that polio was only a disease of the nervous system.²¹

Five years later, however, Sabin, now at Cincinnati Children's Hospital in Ohio, demonstrated that the presence of the poliovirus in the alimentary canals of deceased humans indicated that this canal was in fact the “primary localization

Albert Sabin

Albert Sabin (AAI 1946) was born in Białystok, Poland,²⁰ in 1906. His family immigrated to the United States in 1921 to escape growing violent antisemitism and settled in Patterson, NJ, in the shadow of New York City. In 1923 Sabin enrolled at NYU, earning his bachelor's degree in 1928 and a medical degree in 1931.

His research toward a polio vaccine began years before



Preparing doses of oral polio vaccine
CDC

or portal of entry.”²² Instead of relying on samples sent to his laboratory, Sabin and his assistants personally travelled to morgues in Ohio, Indiana, and West Virginia during an epidemic in 1940 to perform autopsies on every polio fatality they could. Their extreme precautions regarding sterile instruments allowed them to confirm that the poliovirus entered the body via the gastrointestinal tract rather than the nasal route.

As occurred with so many other scientists at the time, Sabin's work on polio was interrupted by the Second World War. He remained focused on virus research, however, developing effective vaccines for three mosquito-borne flavivirus diseases: St. Louis encephalitis, Japanese B encephalitis, and dengue. Much of this research was published in *The Journal of Immunology* (*The JI*).²³

When Enders, Weller, and Robbins developed the technique to culture the poliovirus, Sabin began work on a live-virus vaccine, attenuated by being passed through monkey tissue repeatedly. This oral polio vaccine (OPV) produced immunity faster than the IPV, provided both humoral and cell-mediated immunity, and entered the body by the digestive system just like the actual virus.²⁴

Sabin's first trial, in the winter of 1954–55, was on 30 prisoners at the United States Industrial Reformatory in Chillicothe, Ohio, a federal prison that had held Charles Manson as a young adult.²⁵ The next step was a large-scale field trial, but after the Cutter incident, it was unlikely that Sabin would be able to arrange one in the United States.

OPV Trials Abroad

By the mid-1950s, Sabin was not the only one with a new polio vaccine ready for foreign trials. Koprowski, following small clinical trials in the United States,²⁶ was also searching for a country where he could test his vaccine. In 1956 Ireland agreed to a small clinical trial of children with parental consent in Belfast. Initially the trial went well. The children had no ill effect from the oral vaccine and exhibited a positive antibody response. Unfortunately, some fecal samples from the children showed that the virus regained some potency after it passed through the digestive tract of the trial subjects.²⁷

Two years later, Sabin was able to convince the Soviet Union to allow a field trial of his live-virus vaccine using five times the number of children involved in the Salk trial: 10 million participants, all of whom received the vaccine, with no control group. The USSR had

experienced its first widespread epidemics of polio only after the Second World War, but since then had suffered major outbreaks in all of its republics.²⁸ The OPV, given in a sugar cube, was easier to administer than an injection, and compared to the Koprowski vaccine, had the benefit that recipients would shed weakened vaccine—rather than potent virus—in their stool.²⁹

Research at Annual Meeting and in *The JJ*

At the post-war AAI annual meetings, polio was an increasingly frequent topic of discussion. Two talks at the 1947 meeting, the first AAI meeting held after wartime restrictions were lifted, focused on the recovery of the virus and distribution of antibodies in paralyzed monkeys. The 1949 meeting included three talks addressing comparative studies of the different strains of poliovirus. By 1951 the seven polio talks benefited from the culturing breakthrough, covering a variety of aspects of cultivation as well as attempts to produce immunity. Speakers who presented their research at these meetings included Salk, Sabin, Francis, Youngner, Joseph L. Melnick (AAI 1948), and Robert Ward (AAI 1951).

During the same period, *The JJ* continued to publish many articles on new developments made possible now that the poliovirus could be readily cultured. After the publication of the Enders, Weller, and Robbins breakthrough, 65 articles on polio in *The JJ* came from research funded by the NFIP—about twice as many in nine years as in the previous 17.

Legacy of Polio Vaccines

In 1961, the Sabin OPV was approved in the United States. It overtook the Salk IPV due to its ease to administer and the more robust and longer lasting immunity it provided. These advantages were especially pronounced in countries where polio was endemic: the need for sterile syringes made the IPV unsuitable for mass vaccinations, and the OPV provided immunity in the intestinal tract, which aided in preventing infection by the wild-type strain of the poliovirus.

In 1994, polio was declared eradicated from the Americas thanks to the two vaccines. With the threat of polio almost non-existent, the U.S. government recommended a return to IPV in 1999 to avoid any chance of a recipient contracting polio from the attenuated virus in the Sabin vaccine.³⁰ Since then, the Salk vaccine has remained the standard in the United States. Today, the World Health Organization recommends a combination of the OPV and IPV in areas where polio is endemic or new outbreaks occur.

During the worst polio epidemics of the 1950s, parents were terrified that their children would catch the disease and suffer lasting pain and paralysis or death. They leapt at the chance to

immunize their children even as part of a field trial. Today, as the world begins to benefit from rapidly developed COVID-19 vaccines, many people remain skeptical about receiving them, spurning even those that use the new mRNA technology to produce immunity without exposing the recipient either to killed or attenuated virus.



CDC polio vaccine poster, 1963
CDC

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- ¹⁵ Jacobs, 146.
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“Till a More Favorable Time”

Recalling the Suspension of AAI Annual Meetings, 1943–45

Speed limit sign between Lititz and Manheim, PA, 1942
Library of Congress



When the COVID-19 pandemic forced AAI to cancel IMMUNOLOGY2020™ in Honolulu, Hawai‘i, it was the first time the organization had to abort its scheduled annual meeting—this century. It was not, however, the first time AAI was faced with calling off this celebrated conference. During the Second World War, AAI was unable to meet for three years due to federal wartime travel restrictions.

Today, AAI is a much larger and more complex association, and it is also better equipped to keep immunologists connected in difficult and disruptive times. In this issue, AAI looks back at the first time an unprecedented situation forced the disruption of our annual meeting.

War

When Japan attacked Pearl Harbor and other American military installations in the Pacific on December 7, 1941, Congress officially declared war on Japan the next day. Germany, quickly followed by the other Axis states, declared war on the United States on December 11, and Congress responded in kind hours later. Although the war in Europe had begun more than two years prior, the United States spent those years attempting to stay neutral while secretly aiding the Allies.¹ After Pearl Harbor, the country was suddenly embroiled in a global conflict.



The Parker House Hotel, Boston, MA
Library of Congress

The Last Meeting Before Restrictions

The 1942 meeting was held in Boston, Massachusetts, at the Parker House hotel, famous as the birthplace of both Boston cream pie and its namesake roll, and as the location where future president John F. Kennedy announced his candidacy for Congress in 1946.² In a change from previous years, the meeting was scheduled for only a single day.

Of the 50 scientists who presented research at the 1942 meeting, half were from either the host city of Boston or the states of New York and New Jersey. The rest were from across the country and around the world, including from North Carolina, Illinois, Minnesota, and California, and even São Paulo, Brazil.³ The scientific program was wide ranging, with presentations on various aspects of complement fixation; immunization; protein reactions; and diseases such as tuberculosis, influenza, and polio.⁴

On the morning of April 1, the AAI Council met. The minutes of that meeting show very little indication that the country was rapidly mobilizing for war. The normal business of the association was handled, including electing new members and nominating the next president, Jacques J. Bronfenbrenner (AAI 1920, AAI president 1942–45). The Council approved revisions to the “Note to Contributors” in *The Journal of Immunology (The JI)* and discussed specific style standards for manuscripts—all very normal business. They also voted to accept membership in the Federation of American Societies for Experimental Biology (FASEB) “if and when invited.”⁵

The biggest issue of the meeting arose when Arthur F. Coca (AAI 1916), who had served as editor-in-chief of *The JI* since its founding in 1916 and as secretary-treasurer since 1918, offered his resignation from the latter post. The minutes reflected Coca’s explanation that “on account of his very limited diet, he might be prevented from attending



Jacques J. Bronfenbrenner
Missouri Digital Heritage

meetings held in distant places.” His Council colleagues asked him to postpone his decision “until a suitable successor could be found,” which would end up taking longer than expected.⁶

The only indication in the minutes that things were not right in the wider world was the decision that the project for an International Handbook of Immunology be “tabled till a more favorable time.”⁷

Wartime Rationing

Even before the 1942 meeting, the United States was facing restrictions on the home front as massive mobilization demanded raw materials. In addition to the well-known rations for products such as sugar, meat, nylon, and silk, some of the first rationing standards restricted civilian transportation in order to conserve rubber for production of airplane tires and engine components. The War Production Board banned all civilian automobile sales as of the first day of 1942, and tires were rationed beginning January 5. Within two months after the AAI meeting, a national speed limit of 35 mph was established, as tires were shown to last four times longer at that speed than at 65 mph.⁸ At the same time, gasoline was rationed on the east coast. By the end of the year, gas rationing would be nationwide, with most civilians eligible to buy only four gallons per week.

Traveling across the country to a conference became not only logistically impossible, but unpatriotic as well. Every mile put on a private car’s tires was viewed as stealing rubber from military airplanes. Joseph Eastman, the director of the federal Office of Defense Transportation (ODT), launched an intensive propaganda campaign urging voluntary restriction of unessential travel to avoid necessitating government control of railroad traffic. Even though 1943 had been expected to be a very busy year for travel—14,500 organizations had planned national or state conventions—most groups chose to voluntarily cancel their events to support the war effort.⁹

Missed Meetings

The 1943 AAI annual meeting was supposed to have taken place in conjunction with (or as part of) the FASEB meeting in Cleveland, Ohio, on April 6–10.¹⁰ In keeping with both voluntary and legal restrictions, the AAI Council decided to cancel rather than encourage scientists to travel from points across the continent to Cleveland. Also cancelled was the year’s AAI election, so Bronfenbrenner remained the association’s president until another meeting could take place.

With the war still ongoing in 1945, the White House issued a “Ban on Conventions” that was really a series of requests. Starting in February, all conventions of more than 50 people were to be cancelled, hotels were to refuse reservations for unapproved

Life in the War Years

When the United States entered the Second World War, it was still recovering from the Great Depression that began in late 1929. New Deal programs had helped drop the unemployment rate from a high of 24.9 percent in 1933 to 9.9 percent in 1941. The military enlistment of eligible men and rapid growth of the defense industries quickly brought the unemployment rate down to 4.7 percent in 1942, and it averaged 1.7 percent for the remaining war years.

Jim Crow laws (state and local laws in the South) continued unabated during the war years to enforce strict racial segregation in everyday life while disenfranchising black voters through poll taxes and literacy tests. With far fewer segregation laws, northern states nevertheless imposed de facto segregation as housing discrimination created poor, racially homogenous neighborhoods. The federal government was segregated: all branches of the military continued their 150-plus years of official segregation, just as federal government agencies maintained their segregation that had been officially imposed by President Woodrow Wilson in 1913.



Office of Price Administration gasoline rationing poster by Weimer Pursell, 1943
National Archives

Baseball Continues

Baseball in the United States was far and away the country's biggest sport. A month following the attack on Pearl Harbor, Judge Kenesaw M. Landis, the commissioner of Major League Baseball, wrote to President Roosevelt requesting guidance about the upcoming season for the 16 major league and 320 minor league teams, all whites only.

"If you believe we ought to close down for the duration of the war, we are ready to do so immediately... If you feel we ought to continue, we would be delighted to do so. We await your order."

Roosevelt replied a day later, stating that "it would be best for the country to keep baseball going" because baseball "provides a recreation which does not last over two hours or two hours and a half, and which can be got for very little cost... Here is another way of looking at it—if 300 teams use 5,000 or 6,000 players, these players are a definite recreational asset to at least 20,000,000 of their fellow citizens—and that in my judgment is thoroughly worthwhile."

The war did, however, change baseball by moving more games to the evening in keeping with Roosevelt's request: "I hope that night games can be extended because it gives an opportunity to the day shift to see a game occasionally."

With major league baseball and its minor leagues given a "green light" from the president, the Negro Leagues also continued play throughout the war. With higher



President Franklin D. Roosevelt throws out the first pitch
Franklin D. Roosevelt Library and Museum

employment spurred by the war industries, the leagues saw records in attendance during these years and a revival of the Negro World Series in 1942.

Hundreds of ballplayers from the major and Negro leagues, and thousands from the minors, served in all branches of the military for the duration of the war. Many of them lost their lives.

With so many players overseas, a women's league, the All-American Girls Professional Baseball League, was formed and began games on May 30, 1945. Initially more similar to softball, their game evolved to be virtually the same as men's baseball as the women's athleticism became apparent.

A photograph of a "WAR RATION BOOK TWO IDENTIFICATION" form from the United States of America, Office of Price Administration. The form is filled out with handwritten information. At the top left, the number "756276 BT" is printed. The name "Callahan, Jean" is written in the "Name of person to whom book is issued" field. The address is "Nauvoo, Ohio 5 E 756276". The form includes fields for "City or post office", "State", "Age", "Sex", "Issued by Local Board No.", "Street address of local board", and "Signature of issuing officer". A blue stamp from the "OFFICE OF PRICE ADM." is visible on the right side. At the bottom, there is a "WARNING" section with four numbered instructions regarding the use and return of the ration book.

Ration Book, Ohio, United States, 1942
National Museum of American History

meetings, and all trade shows were to be cancelled.¹¹ Hoping the war would conclude in early 1945, FASEB was once again tentatively planning to hold its annual meeting in Cleveland, May 8–10 if possible. The war dragged on too long to allow it, however, and the AAI Council likewise complied with the government's requests.

The war also delayed AAI becoming a member society in FASEB. The 1942 meeting was the second in a row held in conjunction with the FASEB annual meeting. That year, AAI formally applied for FASEB membership, but approval had to wait for the next FASEB meeting, which did not occur until 1946. Because of the unprecedented delay, FASEB officially backdated the join date of AAI to 1942.

The *Jl*

Although AAI was unable to hold meetings while wartime restrictions were in place, it was still able to contribute to scientific research through *The Jl*, which continued publication without interruption. Much of the research the journal printed was directly applicable to the war effort and, in many cases, was funded by the federal government. (See "*The Jl* in a World at War" in the October 2016 issue of the *AAI Newsletter* for more on wartime publications.)

Back to Business

When Japan surrendered to the Allied forces on August 15, 1945, the process of returning to normalcy on the home front began. The ODT lifted the nationwide 35 mph speed limit only four days later.¹² By the end of the war, 99 percent of the



Gasoline and rubber rationing poster by Association of American Railroads in cooperation with the Office of Defense Transportation
National Archives

stock of passenger automobiles, frozen in 1942, had been allotted. The last of the auto rationing ended on October 30.¹³

In a November 28, 1945, letter to AAI members, Bronfenbrenner announced that the 1946 meeting would go forward as planned in March in Atlantic City, New Jersey. Although the federal restrictions had been lifted, plans for a FASEB meeting until that point had been uncertain because of difficulty securing accommodations.

At the March 12, 1946, Council meeting, the minutes reflected not only the election of Michael Heidelberger (AAI 1935, AAI president 1946–47 and 1948–49) as the first new president in four years, but also a unanimous motion offering Coca, still serving as secretary-treasurer, the Council’s “hearty congratulations, its deep appreciation of his long and faithful services...and its wish that his active interest in the Association continue.”¹⁴

The scientific program of the 1946 meeting returned to a two-day format, with 80 scientists giving 46 talks. Penicillin, which had first been used to treat streptococcal meningitis in 1942, and then extensively in the battlefields of the Second World War, was a major theme of the first session. With the war over, AAI members were investigating how the new antibiotic interacted with a variety of bacteria. Other presentations dealt with antibody formation, anaphylaxis, influenza, and diseases that had been encountered in the Pacific such as dengue fever and malaria.¹⁵

Polio also figured into this meeting. Among the new members elected at the 1946 meeting were two giants in the then-ongoing battle against polio, Albert Sabin (AAI 1946) and Hilary Koprowski (AAI 1946). John F. Enders (AAI 1943, AAI president 1952–53), who was soon to culture poliovirus for the first time, was on the AAI Council but did not participate in the membership voting that year “on account of absence from his office.”¹⁶

IMMUNOLOGY2020™

The necessity of cancelling IMMUNOLOGY2020™ and holding IMMUNOLOGY2021™ as a virtual meeting due to the COVID-19 pandemic was as clear as it was unfortunate. The AAI annual meeting today is of a magnitude much larger and more complex than it was in 1942, but digital communication has ensured that the business of the organization can go on, even during years when world events preclude an in-person meeting, with much less disruption than in earlier times.

References

- 1 In the 1930s, the U.S. Congress had passed a series of Neutrality Acts to keep the country from entanglement in foreign conflicts as hostilities were growing among the great powers in Europe, civil war overtook Spain, and Japan was expanding its empire into mainland China. The Roosevelt administration was able to get around the Neutrality Acts in a number of ways to aid the Allies, including the Lend-Lease programs.
- 2 Kennedy also proposed to Jackie Bouvier (1953) and held his bachelor party (1953) at the Parker House.
- 3 Otto Bier (AAI 1947) was affiliated with the Instituto Biológico de São Paulo, but at the time of the 1942 meeting was at Columbia University on a Guggenheim Fellowship.
- 4 Program of the Twenty-ninth Annual Meeting of the American Association of Immunologists, 1942, AAI Archive, Rockville, MD.
- 5 Minutes of the Meeting of the Council of the American Association of Immunologists, April 1st, 1942, AAI Archive, Rockville, MD.
- 6 Minutes, 1942.
- 7 Minutes, 1942.
- 8 Bradley Flamm, “Putting the Brakes on ‘Non-Essential’ Travel: 1940s Wartime Mobility, Prosperity, and the US Office of Defense,” *Journal of Transport History* 27, no. 1: 79.
- 9 *Civilian War Transport: A Record of the Control of Domestic Traffic Operations by the Office of Defense Transportation, 1941–1946* (Washington: US Government Printing Office, 1948), 84.
- 10 The official record is unclear if the AAI annual meeting would be held at the same location and time as the FASEB annual meeting or would, for the first time, be held as part of the FASEB meeting.
- 11 *Civilian War Transport* 85.
- 12 *Civilian War Transport* 175.
- 13 *Civilian War Transport* 159.
- 14 Minutes of the Annual Meeting of the American Association of Immunologists, March 12, 1946, AAI Archive, Rockville, MD.
- 15 Program of the Thirtieth Annual Meeting of the American Association of Immunologists, 1946, AAI Archive, Rockville, MD.
- 16 Minutes, 1946, Appendix.

Hero Horses in the Fight Against Disease

German technicians drawing blood from horses for diphtheria serum, c. 1895
National Library of Medicine

In the December 10, 1894, edition of the *New York Herald*, a headline announced: “ANTI-TOXINE FOR THE POOR.” After three years of rising death tolls among the city’s children due to diphtheria, the newspaper was making an appeal to its readers for donations to support a new and exciting medical treatment: antitoxin serum.¹

The publishers of the *Herald* pledged \$1,000 to begin the fund drive, and the money began coming in rapidly, doubling the initial pledge in only four days. In daily updates, readers were informed about the science behind the new treatment and the scientists at the Pasteur Institute and the New York City Department of Health who created it. Readers also learned about the crucial role of horses in serum production, beginning a long tradition of recognizing hero horses in the biologics industry.

Diphtheria

Death caused by diphtheria was not uncommon in late 19th century New York City. In the century’s next-to-last decade, two spasms of epidemic diphtheria had ripped through the city, claiming 4,894 and 4,509 citizens in 1881 and 1887 respectively.²

Diphtheria is caused by the *Corynebacterium diphtheriae* bacteria, identified in 1883 by Edwin Klebs, and typically transmitted human to human via respiratory droplets. The bacteria secrete a powerful toxin that damages body tissue, predominantly in the mucosal membranes. Early symptoms are indistinguishable from other infections: sore throat, low-grade fever, malaise, and loss of appetite. But as the disease progresses, the most identifiable symptom of diphtheria appears—first a bluish-white membrane on the tonsils, soon followed by a thick gray-green substance spread over the tonsils, larynx, and nasal tissue. Known as a pseudomembrane, it adheres to tissue and is caused by the release of toxins that increase waste products and proteins.

For patients who do not experience early recovery, the disease progresses to a more critical stage. Toxins can travel to and damage internal organs, including the heart, kidney, and liver, causing neuritis, and obstructing the airway (giving diphtheria its nickname of “the strangling angel of children”). If enough toxin is absorbed, the patient can lapse into a coma. Death can occur in six to ten days.³

Diphtheria was a major cause of illness and death in children, and in 1890 “about one half” of the deaths caused by diphtheria and croup occurred in children under the age of five.⁴ In the 1890 census, diphtheria was the sixth-highest cause of death in the United States for the previous year, behind only consumption (tuberculosis), pneumonia, diarrheal diseases, heart disease, and stillbirth. If deaths caused from diphtheria (27,815) and croup (13,862) are combined (97.75 per 100,000 of population), diphtheria becomes the number four known cause of death.⁵ (In the late 19th century “the majority of cases of death attributed to croup are due to diphtheria of the upper air passages.”⁶)

For comparison, the corresponding death rate in 1890 from diphtheria and croup was, in England and Wales, 28.8; in Ireland, 21.3; in Scotland, 44.0; in Belgium, 56.5; in Prussia, 145.4; in Austria, 120.0; and in Italy, 50.0.⁷



Painting by Richard Tennant Cooper depicting diphtheria in the form of a ghostly skeleton strangling a child, c. 1912.

Wellcome Collection

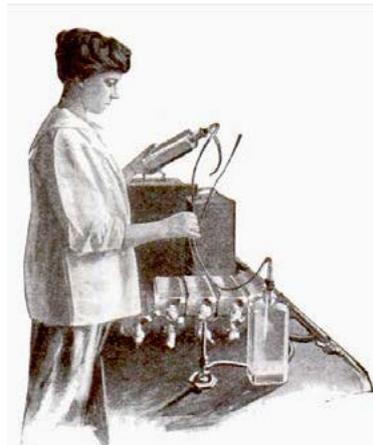


TAKING THE SERUM FROM A HORSE.

Bleeding a Horse for Serum, 1894
New York Herald

Antitoxin

The first successful treatment for diphtheria was the administration of an antitoxin. An antitoxin serum was produced by inoculating horses with small amounts of the diphtheria toxin—enough to immunize without harming the animals. The horses would then be bled periodically. The technician would cool the blood and separate the antitoxin-rich serum from the clotted red blood cells using mouth or mechanical suction. Emil von Behring had discovered this process in 1890, and diphtheria antitoxin produced via a methodology created by Émile Roux at the Pasteur Institute was being used with great success in Europe. The small amounts of antitoxin brought to the United States by individual scientists saved a few lives but could not put a dent in the growing diphtheria problem here.



Preparing the Serum
Popular Science

Diphtheria Antitoxin in New York

At the New York City Department of Health, pathologist Hermann R. Biggs and laboratory director William H. Park (AAI 1916, AAI president 1918–1919) were following the news from Europe about the successes of antitoxin treatment, and along with several other leading physicians and scientists, appealed to the *Herald* to start the fund drive. Their backing prompted many New Yorkers, rich and poor, to make contributions. Nathan Strauss, owner of Macy's, gave \$500, while others gave a dollar or took up small collections at their offices.⁸ World-famous opera singers and actors made significant donations as well.

Just five days after the initial announcement, Biggs, Park, and T. Mitchell Prudden began inoculation of the first horses at the Department of Health, and quickly expanded the antitoxin production facility into new stables that they called the “Herald Annex.”⁹ Park and his new colleague Anna Wessels Williams (AAI 1918) were able to improve upon Roux's method for making diphtheria toxin with

which to inoculate the horses. Williams had compared several different strains and found one that produced as much toxin *in vitro* in one week as Roux's had in a month.¹⁰

By Christmas 1894, 30 horses were busy producing antitoxin. On the first day of the new year, Park administered the first doses of serum treatment to two children at the Willard Parker Hospital, with “favorable reactions,” even though one of the children had not been expected to survive.¹¹

Park immediately began a six-week trial of the antitoxin and demonstrated that when given to patients early in the disease's course, it was effective in stopping further

progression.¹² This success led to the widespread adoption of serum production by municipal health departments in many other American cities.

A year after the initial fundraising appeal went out, the Department of Health passed a resolution acknowledging the contributions of the *Herald* Anti-Toxine Fund, which eventually totaled \$7,496.82, to help begin the production of antitoxin and make it available to the poor of the city.¹³

160

ANIMAL No. 299

Color, Roan

Spec. Yielding Age, 8

Purchased Sept 21/97 200 x 5 Cost, \$ 100.00 Final Disposition, Delivered Dec 25/98

Inoculation No.	Date	Dose C.C.	Remarks	Date	PRODUCT		FORWARDED		DESTROYED	
					No. of Flasks	Quantity C.C.	No. of Bottles	Quantity C.C.	No. of Bottles	Quantity C.C.
1406										
Jan 24	1898	500	2	1898	515	08	2	2000		
Feb 4	1898	500	3	1898	2400	220	08	3	7400	
Feb 10	1898	600	4	1898	3100	400	08	4	7100	
Feb 17	1898	600	5	1898	3400	08	3	6550		
Feb 24	1898	700	6	1898	3700	110	08	3	5700	
Mar 3	1898	700	7	1898	4000	120	08	2	4750	
Mar 10	1898	800	8	1898	4300	120	08	2	4800	
Mar 17	1898	800	9	1898	4600	120	08	2	4800	
Mar 24	1898	900	10	1898	4900	120	08	3	4800	
Apr 1	1898	900	11	1898	5200	120	08	3	4800	
Apr 8	1898	900	12	1898	5500	120	08	3	4800	
Apr 15	1898	900	13	1898	5800	120	08	2	4800	
Apr 22	1898	900	14	1898	6100	120	08	2	4800	
Apr 29	1898	900	15	1898	6400	120	08	2	4800	

Serum Horse Record Book, New York City Department of Health, 1909
National Museum of American History

The St. Louis Antitoxin Tragedy

Following New York's success, St. Louis, MO, set up a municipal diphtheria antitoxin production facility, but lack of careful oversight led to tragedy. A retired milk-wagon horse named Jim provided the serum for the city's antitoxin, which initially proved effective. But at the end of October 1901, May and Bessie Baker, two sisters aged four and six, died after being given diphtheria antitoxin. Their two-year-old brother died a few days later, also after receiving antitoxin treatment. Diphtheria did not kill them, though; they all died of tetanus.¹⁴



Separating the serum from blood by mouth, 1894
New York Herald

The children's doctor, R. C. Harris, had been called to treat Bessie, who was suffering a severe case of diphtheria. He gave the antitoxin to all three children as a precaution. Harris reported the deaths to the St. Louis Health Department and discovered that at least two other children who had received antitoxin from the city supply had also been killed by otherwise unexplained tetanus.¹⁵

Inquest

Officials at the Health Department began an investigation and within days announced that the serum had come from a horse named Jim. The old horse had been inoculated on September 22 and bled on September 30. His handlers recognized signs of tetanus the very next day and euthanized Jim on October 2. According to the Health Department's records, none of the serum from the September 30 blood draw had been distributed or used. Jim had also provided serum on August 24, but at that time he had been in perfect health. All of the serum had been prepared under the supervision of the city bacteriologist, Amand Ravold.¹⁶

By November 5, 11 St. Louis children had succumbed to a painful death from tetanus, and a legal inquest had begun taking testimony. A veterinarian testified that Jim should have been immunized against tetanus, a practice that was "in vogue" at east coast antitoxin facilities. Robert Funkhouser, the city coroner, determined that serum from the September 30 blood draw had in fact been used to produce serum, and furthermore that some of that serum had been mislabeled as part of the August 24 batch. He confirmed through testing that this serum was tainted with tetanus toxin.¹⁷

Surprise Testimony

On November 30, assistant bacteriologist Martin Schmidt finally broke his silence, testifying that Ravold had not tested the serum on guinea pigs before its release. He had kept quiet about this because of his personal friendship with Ravold. Schmidt also implicated Henry Taylor, an African American janitor in the Department of Health, who had been given unlabeled flasks of serum from both blood draws and directed to bring them to Schmidt, with no way to distinguish them but reliance on his own memory. Taylor, of course, had no idea that any of the serum was tainted.¹⁸

The final outcome of the inquest was the dismissal of both Ravold and Taylor. Officially, responsibility for the deaths of 13 children was judged to be Ravold's. Taylor bore no blame for the tragedy, but the inquest commission decided he had obstructed the investigation with contradictory statements during his testimony. No criminal proceedings were recommended.¹⁹

Federal Regulation of Biologics

The tragedy in St. Louis could have been a disaster for the future use of antitoxin, but the inquest clearly showed that the serum itself was not the culprit. Diphtheria remained a dreadful threat to children, and antitoxin was so far the only reliable treatment or preventative. To preserve both safety and public confidence in antitoxins and vaccines, Congress passed the Biological Products Act of 1902, also known as the "Virus-Toxin Law." The Act required federal licensing of facilities producing biologics for interstate shipment, and established safety reviews and approvals before products could be released. Authority to enforce the Act was given to the Hygienic Laboratory of the Marine Hospital Service, which evolved into the National Institutes of Health in 1930.²⁰



DOCTOR AMAND RAVOLD.

Dr. Amand Ravold, St. Louis City
Bacteriologist, 1901
St. Louis Republic

Horses as Heroes

With new national standards for biologics, serum production expanded rapidly to fight not only diphtheria but a host of other diseases. The advances in treatment and immunization could not have happened without the quiet work of the horses who provided serum. They are largely forgotten now, but in their day, many became famous and widely adored for their contributions to health science. Even into the 1930s, only about half of the horses inoculated would produce antitoxin.²¹ Individual horses became heroes for their ability to reliably produce large amounts of potent serum.

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Hero Horses

Throughout the 20th century, horses remained on the front lines as indispensable sources of antitoxin serum against a wide array of diseases. Many of them became well known for their exceptional service. Here we present profiles of a few of these hero horses.



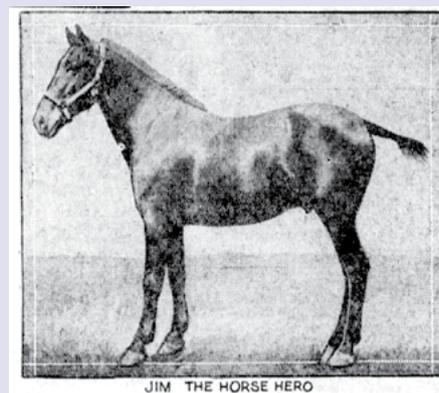
Old Faithful, the "\$175,000 Horse"
Who's Who Among the Microbes

Old Faithful

At the New York City Department of Health, meticulous records were kept on all the horses and other animals used in serum production. Because there were so many, most were officially identified only by a number. Occasionally, however, one would earn a name, like Old Faithful, the "\$175,000 horse" that Park and Wessels featured in *Who's Who Among the Microbes*. While many horses gave blood for only a few years, this former firetruck horse earned his name by supplying enough serum over his long second career to treat more than 20,000 children.

Jim (Mulford)

Not to be confused with the unfortunate Jim of St. Louis, Mulford's Jim assisted Frank M. Huntoon (AAI 1918) with the production of antipneumococcic serum in the 1920s. After pneumonia killed so many during the First World War and the influenza pandemic, an effective treatment for pneumonia was a high priority. Huntoon inoculated Jim with killed pneumococcus bacteria to immunize the horse, and then again with live bacteria to stimulate increased antibody production. Before the era of antibiotics, serum treatment for pneumonia was a revolutionary innovation, reducing mortality by up to two thirds.¹ Huntoon published some of the results of his collaboration with Jim in *The Journal of Immunology*.²



Jim, Mulford's Pneumonia Serum Horse, 1923
Coshocton Tribune

King Hi

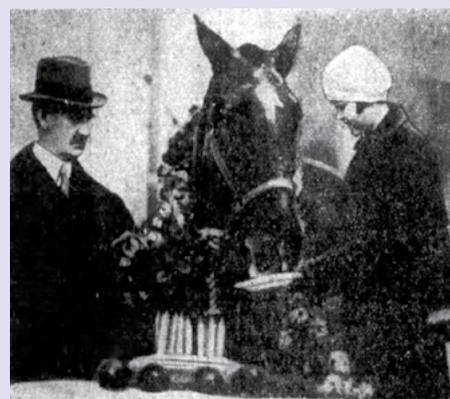
King Hi started life as a racehorse and show jumper. When he developed fistulous withers following an injury in 1930, he entered semi-retirement on the health farm at Michigan State University. There, King Hi was inoculated with both diphtheria and influenza. He produced serum for a few years before he recovered enough to return to athletics. In 1938, King Hi was a champion show jumper for the U.S. Army equestrian team and even qualified for the U.S. Olympic team. Unfortunately, he was never able to compete on the world stage because the 1940 and 1944 summer Olympics were cancelled due to the Second World War.³



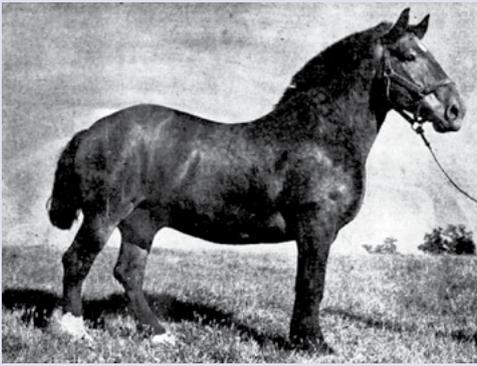
King Hi, ridden by Capt. Royce Drake
Horse Forum

Old Doc Dobbin

The star at pharmaceutical company E. R. Squibb & Sons was a large black Percheron draft horse named Doc Dobbin, who produced over 41,000 doses of diphtheria antitoxin. To celebrate the role of animals in the fight against disease, Squibb Vice President John F. Anderson (AAI 1918) hosted a birthday party for Old Doc on November 9, 1930, attended by children from a local school. In his copious free time, Old Doc "had nothing to do but gallop around the pastures provided for him." When the horse passed away in 1932 at the age of 21, he received glowing obituaries in newspapers across the country, including the *New York Times*.⁴



Old Doc Dobbin at his birthday party, with
John F. Anderson
Ridgewood Herald



Jumbo, 1942
Popular Science

'Jumbo' Donated 450 Gallons of Blood in His Lifetime



Likeness of Famous Horse Preserved for Posterity in Plaque of Barre Granite

Jumbo, 1951
Burlington Free Press

Jumbo

During the First World War, gas gangrene was a serious problem for soldiers in the trenches, and antitoxin would be needed in the next war. At Lederle Laboratories, Jumbo served for 11 years producing antitoxin to treat gas gangrene, as well as for pneumonia and tetanus. Twice a month, his caretakers drew up to two-and-a-half gallons of blood; the rest of his time was spent in leisure. In 1940, the one-ton Belgian draft horse retired to become a pet of the laboratory, and after his death the local stoneworkers' guild presented Lederle with a granite plaque honoring his service.⁵

Next page: See our new history feature, "Material Culture of Immunology," to learn about First Flight, another hero horse.

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BACTERIA EATERS: The “Twort-d’Hérelle Phenomenon”

Electron micrograph of bacteriophages attached to bacterium
Graham Beards

Two decades after diphtheria antitoxin became a clinical success at the end of the 19th century, greatly reducing death from the disease, especially among young children, a new phenomenon with claims of vast therapeutic potential against bacterial infections burst onto the scene. The “Twort-d’Hérelle Phenomenon,” also known as “transmissible lysis of bacteria,” was named after its two co-discoverers: Frederick William Twort and Félix Hubert d’Hérelle. We know it now as bacteriophage.

The Discoveries of Bacteriophage

In 1915 Twort, a British physician and microbiologist, published a paper in the *Lancet* describing a “glassy and transparent” transformation on agar plates where bacteria would not grow even when subcultured. He was able to take samples from the glassy area of the colony and replicate results over multiple generations of micrococcus, demonstrating that the agent was transmissible. These



Frederick Twort, c. 1914
Obituary Notices of Fellows of the Royal Society

samples remained lethal to bacterial cultures even after passing through a fine porcelain filter that would trap bacteria. Further, Twort concluded that the substance required bacteria for growth.¹ He postulated that the micrococcus itself might be secreting an enzyme able to pass through a filter that both caused lysis and stimulated further enzyme production, and that this transmission

“might almost be considered as an acute infectious disease of micrococci.”² Before Twort could conduct further experiments, however, the First World War interrupted his career. As the paper was about to go to press, he joined the Royal Army Medical Corps and was shipped out to Greece. Following the war, Twort moved “on to other work.”³

In 1917, independent of Twort’s research, d’Hérelle, a French-Canadian microbiologist researching enteric bacteria of dysentery patients at the Pasteur Institute, published a short paper in *Comptes rendus de l’Académie des Sciences* describing the lysing of bacteria over multiple propagations.⁴ He named this “invisible microbe that is antagonistic to the dysentery bacillus” the bacteriophage (a bacteria-eater, from the Greek *phagein* meaning “to devour”). D’Hérelle concluded his paper with a few observations: that the bacteriophage is a “microbe of immunity;” it has specificity; and there is a real potential to treat bacterial infections with phage therapy.⁵

D’Hérelle would publish a few more short bacteriophage papers in *Comptes rendus* before publishing his first book *Le Bactériophage: son rôle dans l’immunité* (*The Bacteriophage: Its Role in Immunity*) in 1921. It was this book, and the English translation by Yale University bacteriologist and immunologist George H. Smith (AAI 1918), published by Williams and Wilkins in 1922, that popularized bacteriophage therapy.⁶

The Dominant Theories of Immunity

To understand d’Hérelle’s use of the word “immunity” in his first paper and in the title of his book, it would help to first consider the competing theories of immunity at the time and how the bacteriophage aligned or conflicted with them.



Félix d’Hérelle
Smithsonian Institution Archives

In the late 19th and early 20th centuries, the term immunity was frequently used to describe resistance to “natural” infections, whereas immunity acquired through vaccination was considered something different. And for researchers at the time, “it was not at all clear that ‘natural’ immunity and ‘acquired’ immunity were mechanistically related.”⁷ Further, there were two divergent

theories attempting to explain natural immunity: cellular, associated with Élie Metchnikoff; and humoral, associated with Paul Ehrlich.⁸

Metchnikoff observed that when starfish larvae were punctured with a splinter, cells moved toward the injury and began to engulf foreign bodies. This led him to hypothesize that organisms had specialized cells that were able to defend against intruders. These cells that could identify, engulf, and kill foreign microorganisms were soon named “phagocytes.” In subsequent studies, Metchnikoff was able to observe that phagocytes have specificity as to which foreign organisms they attacked.⁹

Ehrlich’s research about immunity was focused on how animals could acquire immunity against a disease through prior infection or vaccination—vaccines for smallpox and rabies were the only effective ones for humans at the time. It was known that human blood in *in vitro* experiments could agglutinate bacteria as well as a variety of “toxins,” like the one produced by diphtheria. To make sense of what was occurring *in vivo*, Ehrlich

hypothesized, using chemistry terminology, that there were substances (perhaps proteins) in the blood that could act on a specific bacteria or toxin resulting in either “agglutination” (bacteria or other microscopic objects) or “flocculation” (toxins and soluble other substances). He later expanded this theory, once again using chemistry terminology, to try to describe the specificity of the agglutination and flocculation reactions. His addendum that the blood substances were composed of “core” and “side-chains” found some adherents, but subsequent research proved that the complexity of immune cells and substances could not be analogized easily to chemistry concepts.¹⁰

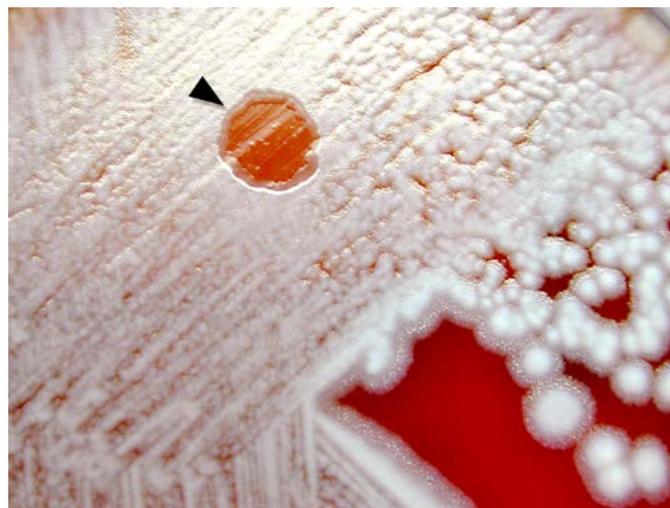
For their theories on the immune system, Metchnikoff and Ehrlich shared the Nobel Prize in Physiology or Medicine in 1908 “in recognition of their work on immunity.” Though both had adherents, in the late 19th century Ehrlich’s humoral theory was put into clinical practice by Émile Roux and Emil von Behring, who created the first successful diphtheria antitoxins and pushed the limits of serum therapy, which was a method to passively immunize humans and animals against specific diseases.¹¹ (See “Hero Horses in the Fight Against Disease,” *AAI Newsletter* October 2021, for more information.) The clinical success of the diphtheria antitoxin raised the stature of Ehrlich’s theory as well as the potential for successfully curing, or even providing acquired immunity, against other bacterial infections.

Bacteriophage Theory

D’Hérelle, however, found that neither the humoral nor cellular theory of immunity fit his experimental observations using bacteriophages as a curative treatment. In experiments

with chickens and humans, d’Hérelle provided results that showed bacteriophage therapy (also called bacteriophagy) could be successful in cases where the specific bacteria were known and the corresponding bacteriophage was provided to the subject. As a result, he proposed a new theory for immunity based on the bacteriophage.

According to historian of science William Summers, d’Hérelle understood “that in natural immunity (as opposed to the ‘artificial’ situation of experimentally induced infections), man and animals resisted and eventually recovered from disease



Petri dish showing where phage suspension has lysed bacteria culture
CDC



Ďe M etchnikoff, 1913
Gallica Digital Library

because of the appearance of phages which destroyed the infecting bacteria.”¹² The evidence d’Hérelle used to support this understanding came from a dysentery study where patients recovering from their infection after the administration of a bacteriophage suspension specific to the bacterium responsible for their infection showed a remarkable increase of the titer of phage in their stool.

A two-phase mechanism for immunity by bacteriophage was described in more detail by d’Hérelle in *The Bacteriophage*. After the specific bacterium responsible for the infection was identified, a bacteriophage specific to that bacterium was put into a suspension, which was then administered to the patient. The first phase, “exogenous immunity,” lasted 24 to 48 hours and was marked by the presence of “bacteriophage protobes virulent to the pathogenic bacterium.” The second phase, “endogenous immunity,” could last up to 14 months and was a response to a “stimulus being provided by the products of bacterial dissolution as contained in the bacteriophage suspension.” During an epidemic, the exogenous phase is maintained because the near constant reinfections maintain the bacteriophages.¹³

For d’Hérelle, the bacteriophage, not a cellular or humoral response, was responsible for immunity, and by 1926 he was certain that bacteriophagy could be used to successfully treat bacillary dysentery, staphylococcus infections, and, potentially, bubonic plague.

Jules Bordet



Jules Bordet, nd.
National Library of Medicine

A major problem for this theory was presented by Jules Bordet (AAI 1960). In the interim between d’Hérelle’s first bacteriophage article and the publication of *The Bacteriophage*, Bordet was awarded the 1919 Nobel Prize in Physiology or Medicine “for his discoveries relating to immunity.” The director of the Pasteur Institute in Brussels, Bordet had spent decades researching

and describing the lysis process in vitro and in vivo. These included the discovery of complement, the development of complement fixation tests, the identification of the bacterium that causes whooping cough, and advances in understanding the bacteriolytic and hemolytic effects in vivo.

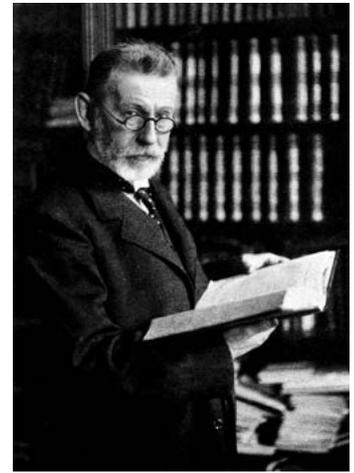
Lacking sufficient magnification to see the bacteriophage, researchers could only understand it by observing its effects, fueling intense debate about what exactly the bacteriophage was—a lysing enzyme (Bordet) or a “microbe of immunity,” perhaps a virus (d’Hérelle)—and how it fit into the competing theories of immunity. As strange as it may seem today, Bordet’s concept of the bacteriophage as a “self-perpetuating lytic enzyme” fit neatly into the humoral theory and serum therapy and carried the prestige of a recent Nobel laureate.¹⁴ It would remain the dominant theory until advances in electron microscope magnification in the late 1930s.

Proliferation of Bacteriophage

The controversy surrounding the bacteriophage did not prevent the proliferation of corresponding research and clinical therapies. The success of diphtheria antitoxin provided a lesson in combatting bacterial disease with a humoral-based serum therapy. The hope was that the new phenomenon would pave the way for additional serum therapies for other bacterial infections in humans and animals.

While the vast majority of the early research with bacteriophages occurred in Europe (most notably in Paris, Brussels, and London), American researchers began publishing on the topic by the early 1920s, even prior to the translation of *The Bacteriophage*.

The first American institution to take bacteriophage seriously as a research topic was the Department of Bacteriology at the University of Michigan, chaired by Frederick G. Novy (AAI 1920, president 1924–25). Novy, who received his first shipment of bacteriophages from d’Hérelle in 1921, collaborated on this research with younger investigators in his department, including Paul de Kruif (AAI 1921) and Philip Hadley (AAI 1927).¹⁵ Hadley would go on to make significant contributions to bacteriophage research in the 1920s and 1930s. De Kruif left Michigan a year later for a position at the Rockefeller Institute for Medical Research (RIMR). He drew on his experiences with his mentors at both institutions when he collaborated with Sinclair Lewis on the best-selling novel



Paul Ehrlich
National Library of Medicine

Arrowsmith.¹⁶ (See “Paul de Kruif and Microbe Hunters,” *AAI Newsletter* January/February 2019, for more information.)

At RIMR, de Kruif shared a laboratory with André Gratia, a Belgian microbiologist who came to the institute in 1920 to study bacteriophages. Gratia soon published papers on his discovery of a bacteriophage capable of infecting staphylococcus and *E. coli*.¹⁷ Gratia returned to Belgium in 1921 but had left an indelible mark on de Kruif. Gratia’s research was mirrored by that of the protagonist Martin Arrowsmith—both were pioneers in phage research and both discovered phages that would lyse staphylococcus.¹⁸

Bacteriophage research would continue at RIMR and get a boost with the arrival of Jacques J. Bronfenbrenner (AAI 1920, president 1942–46) in 1923. Bronfenbrenner began a decades-long study of bacteriophages to explain their physical properties and understand and control their lysis. (Five years later, Bronfenbrenner accepted an appointment as chair of the Department of Bacteriology and Immunology at the Washington University School of Medicine in St. Louis and continued his phage research.)

1920s and AAI

Already widely investigated in Europe by the mid-1920s, bacteriophage research was sprouting up in laboratories beyond Ann Arbor and New York City. A survey of articles published in *The Journal of Immunology (The JI)* in the 1920s reveals phage research programs at Loyola University School of Medicine (Chicago), Baylor University, Yale University School of Medicine, and Stanford University. Compared to similar journals, such as the *Journal of Experimental Medicine*, *The JI* seems to have taken a cautious approach to publishing bacteriophage research, with a mere eight papers published during the decade. Likewise, it was not a topic featured prominently at the American Association of Immunologists (AAI) annual meetings; only two speakers on the subject presented their research: Emil Weiss (AAI 1928), “The Bacteriophage Anti-bacteriophage Reaction,” in 1927; and D. M. Cowie and Henry G. Poncher, “Observations on the Intestinal Bacteriophage in the Specific Infectious Diseases,” in 1928.¹⁹

1930s

The pace of phage research and phage therapy trials continued to accelerate well into the 1930s, but signs of problems with bacteriophage therapies were becoming more evident. Although bacteriophage therapy was “being widely used for many types of bacterial infection,” at the time, there were neither clear guidelines for clinical trials—the familiar control groups and double-blind studies were decades in the future—nor for the standardization of materials and methods.²⁰ Considering the fact that scientists continued to debate whether bacteriophages were enzymes or viruses,²¹ it is understandable that the clinical studies were unable to generate accurate data on dosage, safety, and efficacy.

**THE ORIGINAL
BACTERIOPHAGES**

prepared by
Laboratoire du Bacteriophage, Paris
(under the scientific direction of Professor d’Herelle)

are now available in the following forms:

BACTÉ-PYO-PHAGE
BACTÉ-STAPHY-PHAGE
BACTÉ-INTESTI-PHAGE
BACTÉ-COLI-PHAGE
BACTÉ-RHINO-PHAGE
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Advertisement of bacteriophages
National Library of Medicine

D’Hérelle emphasized that the crucial step in successful bacteriophagy was matching phage strain to the specific bacterial infection. This process, however, was both time consuming and labor intensive for individual clinical cases and exacerbated by the paucity of readily available phage strains. In an attempt to remedy part of this problem, pharmaceutical companies, including Eli Lilly & Co., E. R. Squibb & Sons, and Swan-Myers (a division of Abbott Laboratories), were “manufacturing bacteriophage and offering it to the medical profession.” A *Journal of the American Medical Association (JAMA)* review of the Lilly, Squibb, and Swan-Myers phage preparations demonstrated the lack of standards—including the amount of preservatives or lack thereof, virulence, and mixture of different phage strains—and marked a further move away from d’Hérelle’s ideal bacteriophagy.²²

AMA Phage Report

Criticism of the purported successes of bacteriophagy increased in the early 1930s with titles such as “Limitations of Bacteriophage Therapy” appearing in journals.²³ At this time, the American Medical Association (AMA) Council of Pharmacy and Chemistry, founded in 1905 to advocate for clinical experimentation and evaluate the “chemical identity and efficacy of drugs in humans,” began a review of bacteriophagy in scholarly literature.²⁴ The first report was published in 1934, authored by two Yale University professors: immunologist and bacteriologist Stanhope Bayne-Jones (AAI 1917, president 1930–31) and infectious disease specialist Monroe Eaton (AAI 1937).

The report, “Bacteriophage Therapy: Review of the Principles and Results of the Use of Bacteriophage in the Treatment of Infections,” was published across three issues of *JAMA* in December 1934.²⁵ In the report, the demonstrable ability of bacteriophage to lyse bacteria in vitro was recognized, but those results did not carry over into in vivo studies.

The authors reached the conclusions that “lytic action in the body is inhibited or greatly impeded by blood and other body fluids”; that the “therapeutic action” of the components mixed with the phage before injection needs additional study; that the literature “reveals that the evidence for the therapeutic value of lytic filtrates is for the most part contradictory”; and that “there is no evidence that lysis or killing of bacteria by bacteriophage occurs in vivo.”²⁶

Of particular interest is an additional conclusion reached by the authors: to accept that the “facts appear to indicate” bacteriophage is “inanimate, possibly an enzyme,” though they do leave the door open that it could be a virus. Bordet publicly tried to keep that door closed, stating during the prestigious Croonian Lecture in 1930 that the “invisible virus of d’Hérelle does not exist.” It is the bacteria themselves, subjected to the lysis, which reproduce the lytic principle. Bacteriophagy is accordingly a case of autolysis.²⁷ The Bordet theory about the nature of the bacteriophage remained dominant in the American scientific community.²⁸

The conclusions of the report, however, did not stop bacteriophage research and publication of results—better studies might be more successful. Indeed, phage research continued to spread, with new adherents

like F. Macfarlane Burnet (AAI 1961), a young Australian researcher in England who would decades later win the Nobel Prize in Physiology or Medicine for discovering “acquired immunological tolerance.” While his phage research did not spawn breakthroughs in therapy, it did give Burnet insight into specificity, mutation, and resistance.²⁹

1930s and AAI

In the 1930s, *The JI* continued its conservative publication of articles related to bacteriophage research with only seven papers. One of these, however, directly challenged some of the conclusions of the AMA report. In their 1935 article “The Adaptation of a Staphylococcus Bacteriophage to an Artificially Produced Anti-Bacteriophagic Serum,” d’Hérelle and Morris L. Rakieten, who conducted bacteriophage research together at Yale University, disputed the claim that in vitro bacteriophagy was uniformly diminished by human serum and showed instead that some strains of bacteriophage were able to maintain lysis successfully in the presence of serum.³⁰

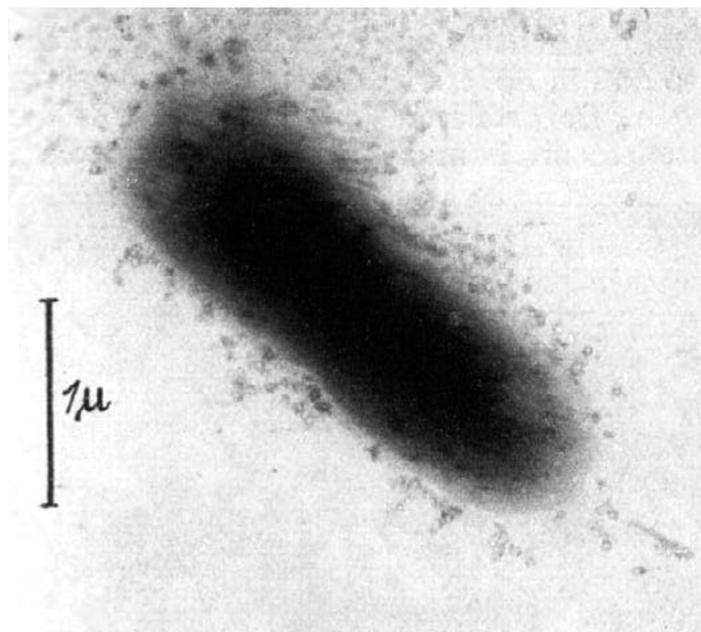
The AAI annual meetings at this time had a dearth of bacteriophage research with only two talks on the topic: Frances C. Frisbee and Ward J. MacNeal, “Therapeutic Application of Bacteriophage in Staphylococcus Bacteremia,” in 1932; and Philip Levine (AAI 1925) and Arthur W. Frisch (AAI 1938), “The Specificity of Multiplication of Bacteriophage,” in 1935.³¹

The Decline of Phage Therapy

The issues of bacteriophagy outlined in the Bayne-Jones and Eaton *JAMA* report were clearly not insurmountable to the dedicated phage researcher, despite failure to demonstrate a successful therapy. What eventually moved the field away from phage research was the advent, expansion, and demonstrable

success of sulfa drugs in the 1930s. Prontosil, patented in 1932, was cheaper and easier to produce and was effective against a wider variety of bacterial infections than bacteriophage therapy. Its success spawned a rush to put new sulfa drugs (and other antimicrobial chemotherapies) on the market.

In 1939, with Europe once again engulfed in a world war, non-war research ground to a halt. The United States would enter the war two years later, and scientific research likewise was quickly refocused to the war effort.



First electron micrograph of a bacteriophage
Naturwissenschaften

In pre-war Germany, the electron microscope was developed and, before the war broke out, achieved sufficient magnification to capture the first images of viruses. When a bacteriophage sample was placed in the microscope in 1939, the picture that developed vindicated d’Hérelle—the bacteriophage was a virus. The image was published in a German scientific journal the following year. Due to the war, however, it would be a few years more before the debate was put to rest.

Bacteriophage therapy research did not end in the 1930s. It continued into the 1940s in the United States and Europe, only to finally be shelved in the archive following the discovery and development of antibiotics. D’Hérelle did continue his research in Ukraine, where, after the war, the Soviet Union had a national program dedicated to phage therapy.³²

Experience with bacteriophages altered the career trajectories of some researchers, including a young Alfred Hershey (AAI 1942) under the mentorship of Bronfenbrenner at Washington University. The lessons learned from studying the bacteriophage helped usher in a new field of biology following the war: molecular biology.

The JI and talks at the annual meetings told a different story for AAI. Evidence points to a conservative approach to bacteriophage research. Whether reflecting the fact that bacteriophages themselves were still not fully understood or that fundamentals of the immunological response to bacterial infections were still in dispute, it seems a cautious approach in the literature and at meetings proved a successful tack for the association and the field.

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A Brief History of Immunology in Portland

Aerial view of Willamette River with Morrison, Burnside, and Steel Bridges, 1915
Portland City Archives

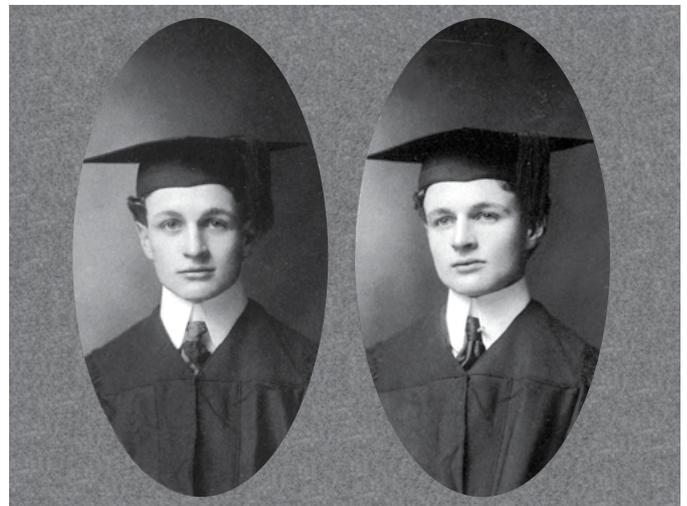
When AAI was founded in 1913, the city of Portland, Oregon, was experiencing rapid growth—the population had doubled in the previous 10 years, making it the fifth largest city in the West behind San Francisco, Los Angeles, Seattle, and Denver.¹ Founded 16 years before the outbreak of the American Civil War, its growth was owed to its strategic proximity at the confluence of the Columbia and Willamette Rivers to the agricultural Tualatin Valley and easy access to the Pacific Ocean via the Columbia River.

For hundreds of years prior to European exploration and settlement of the area, the location proved beneficial for the native communities. It served as the site of villages of the Multnomah, Kathlamet, Clackamas, bands of Chinook, Tualatin Kalapuya, Molalla and other tribes and bands of native peoples. By the mid-19th century, most Native Americans in Oregon were forced onto reservations. Following the forced relocation, a series of federal laws, notably the General Allotment Act of 1887 (referred to as the Dawes Act), were designed to permanently remove and/or assimilate Native people.²

In the first decade of the 20th century, Portland was endeavoring to shake its reputation as a filthy, dangerous town that still possessed a significant amount of Old West miner character. It hosted the 1905 Lewis and Clark Centennial Exposition; three of the bridges across the Willamette River that connected the city and gave it the nickname of “Bridgetown” had been built; and visitors could take a two-and-a-half-hour trolley tour around all the latest, most modern sights.

The Matson Twins

In this booming port city, one physician scientist joined AAI as a charter member. Ralph C. Matson (AAI 1913) and



Ralph (left) and Ray (right) Matson's graduation photos, UO Medical College, 1902

OHSU Digital Collections

his twin brother, Ray W. Matson, were born in Brookville, Pennsylvania, in 1880 and moved as children to Oregon. The twins lived parallel lives, both graduating from the University of Oregon Department of Medicine in 1902 and interning at Portland's Good Samaritan Hospital until 1905. They both did postgraduate studies at various European hospitals and universities, as was common at the time.³ At St. Mary's Hospital in London, Ralph worked under Almroth Wright (AAI 1914) and alongside Alexander Fleming (AAI 1914) in the bacteriology laboratory.

In 1909, the Matson brothers began positions at the first tuberculosis facility in the Pacific Northwest, the Portland Open Air Sanatorium. Ralph served as a bacteriologist, and Ray worked as a pathologist. Within three years, the twins were made co-directors of the sanatorium, just as the state was



Ralph Matson prepping for surgery
OHSU Digital Collections

pushing to make all tuberculosis sanatoria public. They advised the state on a comprehensive public health plan to fight the “white plague” with a combination of public and private institutions.⁴ The brothers were liberal in their use of x-ray technology before the dangers of radiation were fully known; one surgeon could only tell the twins apart by the distinctive patterns of x-ray scars on their hands.⁵

Ralph Matson was a logical candidate to be a charter member of AAI: he was a pioneer in the clinical treatment of tuberculosis, which was in its infancy. Other tuberculosis researchers among the charter group included the first president of AAI, Gerald B. Webb (AAI 1913, president 1913–15), and Karl von Ruck (AAI 1913).⁶

Like other early AAI members, including future AAI president Stanhope Bayne-Jones (AAI 1917, president 1930–31), Matson went to France in 1916 to join the British Expeditionary Forces (BEF) prior to American involvement in the First World War. He was reunited with Wright, now the consulting physician for the BEF, who requested his service at the research laboratory established at Boulogne-sur-Mer, France.⁷

After the war, the Matson brothers returned to the sanatorium. Ralph lectured to crowds of thousands about his experience in the war. He became one of the greatest thoracic surgeons of his era and remained active both in private practice and as a teacher at the University of Oregon Medical School until his death in 1945. Ray died in a spectacular manner in 1934 when his sports car, driven by fur coat model Jeanne Ingalls, crashed into a concrete barricade on Portland’s Burnside bridge at 2:30 a.m.⁸

Growth of Portland Medical Research

Since the earliest days of the city, biomedical research in Portland has centered on the Oregon Health & Science University (OHSU). Established in 1887 as the University of Oregon (UO) Medical Department, it was the first medical school in the Pacific Northwest. A merger with the medical education program of Willamette University formed the University of Oregon Medical School, and in 1974 it became an independent institution.

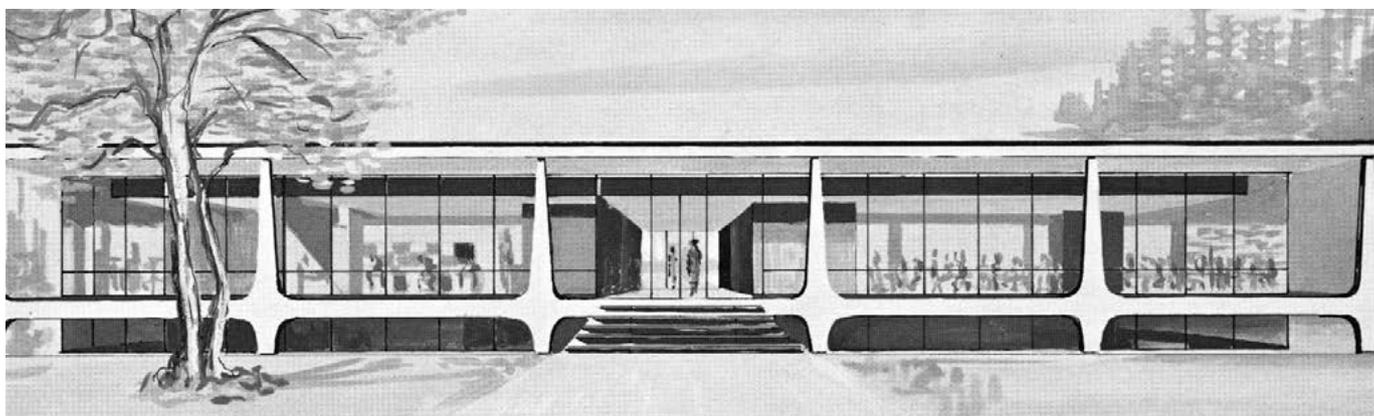
After Matson, there were no AAI members in Portland until Arthur W. Frisch (AAI 1956), who joined the faculty of UO Medical School as professor of bacteriology in 1946 from Wayne State University.⁹ He became chair of the Department of Bacteriology in 1956 and served in that capacity until 1972. Frisch’s main research interests were serotyping and the legal aspects of blood groups. He was known as an immunologist to his coworkers in the bacteriology department.¹⁰

In 1962, with a \$1.9 million grant from the National Institutes of Health, the Oregon National Primate Research Center began operations outside Portland with the OU Medical School as its host institution.¹¹ There, the hundreds of monkeys, apes, and other primate specimens were used in a wide range of research in four major areas: reproductive biology, cardiovascular and metabolic disease, cutaneous biology, and immune diseases. Arthur Malley (AAI 1969) joined the staff in 1964 and conducted research in immunology and biochemistry until his retirement in 1995. In addition to his research at the primate center, Malley taught immunology at Reed College for a number of years.

The Oregon state legislature changed the name of the UO Medical School to Oregon Health Sciences University in 1981.¹² By that time, AAI members were represented there in several specialties, including pathology, ophthalmology, and dermatology, in addition to the Department of Microbiology and Immunology. In 2001, the university merged with the Oregon Graduate Institute and the new institution was named the Oregon Health & Science University.



Aerial view of the University of Oregon Medical School, c. 1940–48
OHSU Digital Collections



Architectural rendering of the Central Services Building, Oregon National Primate Research Center
OHSU Digital Collections

Independent Research in Immunotherapy

Of the many independent research institutions in the Portland area, the one that has had the largest AAI representation is the Earl A. Chiles Research Institute, today part of the Providence Cancer Institute in Portland. Established in 1987 for general medical research, it became primarily focused on cancer research in 1993 when Walter J. Urba (AAI 1988) was recruited from the National Cancer Institute to become its director—a position he still holds today.

By 1996, an early human trial of a breast cancer immunotherapy using an alleogenic cell line and CD80 was conducted by Urba and Deric Schoof (AAI 1990).

While no vaccine was developed from that trial, the study did show immunizing effects that would inform later studies.¹³ The Chiles Research Institute continues to conduct important basic research and develop promising cancer immunotherapies.



Front Avenue, Portland, 1910
Portland City Archives

IMMUNOLOGY2022™ in Portland

At the 105th annual meeting in Portland, you will have the opportunity to learn much more about the history of immunology in Oregon and the surrounding region. We hope you will visit the AAI History Exhibit to learn more about the significant contributions made to the field by AAI members living in the West!

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HISTORY

VALUABLE EXPERIMENT
PLEASE DO NOT DISTURB
MONTANA STATE BOARD
OF ENTOMOLOGY
HAMILTON, MONT.

Rocky Mountain Laboratories: An Outpost of Immunology

Notice of ongoing ecological study in Hamilton, Montana, 1928
Office of NIH History

From a humble beginning in an old schoolhouse in Montana, the Rocky Mountain Laboratories (RML) have become a premier research hub and an integral part of the National Institutes of Health (NIH). Many significant scientists in the U.S. Public Health Service (PHS) and AAI came through the lab or made it their long-term research home.

Rocky Mountain Spotted Fever

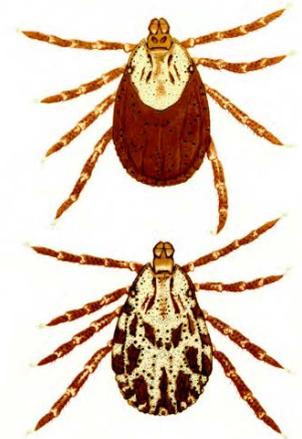
As European settlers moved west into the northern Rocky Mountains and began to colonize the area that would become Montana, they began to experience outbreaks of a new deadly disease of unknown origins.

This malady was named for the telltale, distinctive dark measles-like rash all over the body and dangerously high—and sometimes weeks-long—fever. It could also produce a variety of additional symptoms, including neck stiffness, body aches, vomiting, diarrhea, inflammation of major organs, gangrene of the toes and fingers, and neurological issues such as severe headaches and confusion. Prior to the creation of effective treatments, those who were infected faced long-term complications like liver damage, hearing

loss, neurological deficits, and partial paralysis. Once the rash presented, the disease was fatal in up to 80% of cases.¹

Originally referred to as “black measles,” it became commonly referred to as Rocky Mountain spotted fever (RMSF), especially after the 1890s, when frequent outbreaks occurred in the Bitterroot Valley of southwest Montana.²

By the turn of the century, RMSF was a significant enough problem that the newly formed Montana State Board of Health (MSBH) made it one of its first priorities. In February of 1902, MSBH agreed to investigate cases as soon as they appeared that spring. When those first cases emerged, a Great Falls physician named Earle Strain noticed a tick on one of the victims. Strain, who had been to Europe to study bacteriology, was aware of recent discoveries of arthropod vectors for disease and advised the Board of the tick’s potential role in transmission.³



Rocky Mountain wood tick,
Dermacentor andersonii
Rocky Mountain Laboratories



ERUPTION OF TICK FEVER.

Illustration of RMSF rash by John F. Anderson, 1920
Rocky Mountain Laboratories

The First Labs

Working out of temporary laboratory quarters in a local hospital, MSBH researchers, with the help of the PHS,

began a two-pronged approach: physicians gathered epidemiological data on all cases, while pathologists examined the tissues of spotted fever sufferers. By the summer of 1902, an unknown parasite was regularly seen in the red blood cells. This evidence, coupled with the timing of the disease to correspond with the annual emergence of ticks, seemed to confirm Strain's suspicions.⁴

At the beginning of the 1903 tick season, bacteriologist and future director of the PHS Hygienic Laboratory John F. Anderson (AAI 1918) arrived in Montana.⁵ He examined the collected epidemiological data and decided that it all supported a tick vector: cases correlated with activities that involved likely exposure to ticks. Nearly all patients had a history of tick bites a week before the onset of spotted fever.⁶ Comparing the blood-borne parasites with those of malaria and Texas cattle fever, he found similarities that further supported a bacterial agent transmitted by a tick. He was so sure of this finding that he suggested renaming the disease "tick fever."



A staff member, possibly Ralph Parker, sweeps for ticks, c. 1920
Office of NIH History

To prove the tick hypothesis, MSBH staff went tick hunting. They dragged large white cloths across the Montana scrublands to collect countless ticks and other possible vectors for study. One of the likely suspects found during these collections, the Rocky Mountain wood tick, was named *Dermacentor andersoni*, after Anderson, in 1908.⁷

Identifying the Agent

In 1906, Howard T. Ricketts, then a University of Chicago pathologist, came to Montana to perform research on tissue samples from spotted fever patients. His laboratory was no more than a tent on the grounds of the Northern Pacific Hospital in Montana.⁸ By using guinea pig models, he was able to study the disease year-round, not only during tick season.

The breakthrough came when Ricketts inoculated several guinea pigs with either washed cells, serum, or filtered serum, from one nine-year-old patient. When only the guinea pigs injected with filtered serum avoided infection, he knew the agent had to be a blood-borne bacte-



The tent laboratory of Howard Ricketts, 1906
Office of NIH History

rium and not what was then known as a filterable virus.⁹ Ricketts had identified a new class of vector-borne obligately intracellular bacteria that became known as *Rickettsia rickettsii*.¹⁰ The bacterium responsible for RMSF was described as *Rickettsia rickettsii*.

Ricketts also conducted an experiment on transmission somewhat similar to the one by Theobald Smith (AAI 1920) in Texas that first established ticks as a disease vector. He took ticks from infected guinea pigs and transferred them to healthy ones, which then showed signs of spotted fever.¹¹ This confirmed the tick transmission theory once and for all.

Public Health Measures

Armed with this new knowledge, research into prevention and cure for RMSF could begin. After 1910, the Montana State Board of Entomology began a cattle-dipping program to kill ticks on livestock with a quick bath in an arsenic solution. Public health officials educated locals about the tick menace and how to protect themselves from exposure.

The Schoolhouse Laboratory



The two-story empty school building in Hamilton, Montana, which in 1922 became RML, 1925
National Library of Medicine

The earliest labs that would become the RML were temporary structures or borrowed woodsheds. Only in 1921 did Ralph Parker, an entomologist assigned by the PHS, secure an abandoned schoolhouse on the Bitterroot River as a more stable home for research. At the "Schoolhouse Lab," the research teams kept



Ralph Parker and his wife Adah Parker on their honeymoon conducting tick research, 1916
Rocky Mountain Laboratories

countless live ticks, all collected from the countryside and painstakingly catalogued by species, source, and life cycle stage. Parker and Roscoe Spencer managed to produce the first effective vaccine against RMSF in 1924 by emulsifying tick tissue and killing the bacillus with phenol.

Green Light



Green Light novel and film adaptation

The struggle to defeat RMSF at RML was dramatized in the 1937 film *Green Light*, starring Errol Flynn as a wrongly disgraced surgeon who goes to Montana to research spotted fever. There, he falls victim to the disease and receives an experimental dose of the vaccine. Based on a best-selling novel by Lloyd C. Douglas and inspired by the actual scientific endeavor, *Green Light* was well received by critics and at the box office, showing

that a scientific drama could captivate audiences.¹²

Expansion of the Laboratories

In 1928, Montana finally approved funds for a new permanent facility in the town of Hamilton. Through the 1930s, the RML grew from a single building and 26 employees to a federally owned and operated campus of seven buildings and more than 100 staff, including virologists, bacteriologists, and parasitologists.¹³ In 1937, RML became part of the NIH.¹⁴

Wartime Vaccine Production

The Second World War transformed RML from a regional research center into an essential vaccine production



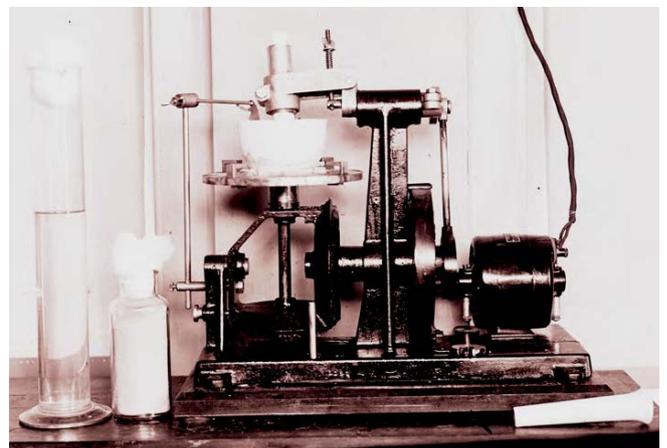
Researcher Emily Emmart working in RML, c. 1937
National Library of Medicine



Shepherds in Idaho receiving RMSF vaccine, 1926
Rocky Mountain Laboratories

facility. Using seed virus from the Rockefeller Institute and serum donated by students at Montana State University in Missoula,¹⁵ RML began producing the yellow fever vaccine in February 1941. When the United States was drawn into war in the Pacific after the attack on Pearl Harbor later that year, vaccines against yellow fever and other tropical diseases became an essential part of military readiness, administered to every member of the armed forces.¹⁶

Two researchers at RML, Mason Hargett and Harry Burruss, developed their own novel yellow fever vaccine in 1941 that did not rely on human serum. After several lots of the Rockefeller vaccine were found to be contaminated with hepatitis B, the Hargett-Burruss vaccine, produced with chick embryo protein in an aqueous base, became the standard vaccine for the U.S. Army by May 1942.¹⁷ Throughout the war, RML was also a vital production site for vaccines against RMSF and typhus.



Automatic tick grinder to prepare the large volumes of tick tissue necessary for vaccine research, 1931
Rocky Mountain Laboratories

Vaccine Innovations

After the war, RML remained an important research site. John J. "Jack" Muñoz (AAI 1951) and his team were instrumental in the development of acellular vaccines that use only a part of the bacterial agent to induce immunity. Working with *B. pertussis* in the 1970s and 80s, this group

of researchers isolated the piece of DNA that contained the genes for pertussis toxin, eventually making possible the pertussis vaccine that is included in today's DTaP vaccine.¹⁸

RMSF and RML Today

Today RMSF is found in the United States, Mexico, Canada, and Central and South America. In the United States, 60% of the cases are from five states—North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri—though it can still be found in the area where it was first discovered. When treated early with antibiotics (typically doxycycline) and palliative care, symptoms diminish within a few days and patients make a full recovery. In the United States, in addition to the Rocky Mountain wood tick, the American dog tick and the brown dog tick have been discovered to serve as vectors for RMSF.

The RML continue to produce important and innovative basic research into a wide array of human and livestock diseases, including mad cow disease, Lyme disease, Q fever, and SARS-CoV-2. The facility, now comprising 30 buildings on 36 acres, features BSL-4 laboratory space equipped to handle the most dangerous infectious organisms—a far cry from the tent laboratories where the earliest discoveries were made.



Immunologists at the Rocky Mountain Laboratory
National Library of Medicine

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Blue Bloods: Bang, Levin, and the Horseshoe Crabs

Horseshoe crabs coming ashore to spawn
Greg Breece, US Fish and Wildlife Service

For almost half a billion years, this planet has been home to a strange creature that looks like something from another world and whose blood has become a precious commodity. Horseshoe crabs, arthropods that comprise the family Limulidae, are shallow-water animals protected by a round carapace about a foot across that covers most of their body, with a long, spiny tail dragging behind. Flip them over, and you'll find 10 legs and a gill assembly.

Inside these odd animals is a circulatory fluid that has proven invaluable for pharmaceutical testing for decades—recently, by ensuring the purity of the COVID-19 vaccines.

First Looks at the Horseshoe Crab

At the turn of the 20th century, when scientists began investigating the blood of *Limulus polyphemus*, the Atlantic horseshoe crab, some of the earliest research was stymied by the blood's propensity for quick coagulation. In 1908, Carl Alsberg and Ernest Clark decided to study the clotting mechanism itself. They found that the clot was formed of a substance they called cell fibrin, whose chemical composition was initially perplexing.¹ It was practically insoluble in all but the most caustic alkaline solutions.

The chemical that makes horseshoe crabs' blood blue is hemocyanin, a copper-protein, oxygen-transporting compound also found in many crustaceans and mollusks. Unlike hemoglobin, which is a component of the red blood cells of vertebrates,² hemocyanin is an extracellular compound floating freely in the circulatory system.

Alsberg and Clark had access to abundant populations of Atlantic horseshoe crabs at the U.S. Bureau of Fisheries Woods Hole Marine Biological Laboratory (MBL) on Cape Cod, Massachusetts.³ In the early summer, typically during spring neap tide, countless horseshoe crabs crawl onto the



A horseshoe crab on the beach at Monomoy National Wildlife Refuge, Massachusetts
Bill Perry, US Fish & Wildlife Service



The Marine Biological Laboratory at Woods Hole
Falmouth Public Library

HISTORY

beach to spawn and nest, leaving millions of tiny eggs in the sand. Juvenile crabs spend their first two years in the shallow intertidal waters before moving into deeper water until it is time to spawn.

The researchers could get up to 400 cc of blood out of a single crab by pumping the two halves of its body “like opening and closing a bellows.”⁴ Comparative studies quickly showed that the hemocyanin of *Limulus* was distinct from that of other invertebrates such as octopus. Alsberg eventually demonstrated that aside from hemocyanin and the clotting protein, there was almost no other protein matter in the blue blood.⁵

Limulus in *The JJ*

After Karl Landsteiner (AAI 1922, president 1927–28) described human blood groups in 1901, comparative studies of the blood of various species filled biomedical journals, including *The Journal of Immunology (The JJ)*, and *Limulus* blood was not left out. The first mention of horseshoe crabs in *The JJ* appeared in 1920, when Carl Schmidt showed that hemocyanin, unlike hemoglobin, is antigenic in mammals. Although Schmidt was working with hemocyanin derived from abalones, he interpreted earlier research with an immunological perspective, identifying the *Limulus* hemocyanin reaction seen by Alsberg and Clark as globulin-like behavior.⁶

Bang's Discovery



Frederick B. Bang
AAAS

In 1953, a researcher from Johns Hopkins University was spending a summer at the MBL studying horseshoe crabs, just as Alsberg and Clark had decades before. Frederick Bang (AAI 1953) noticed a strange reaction in the crabs' already unusual clotting mechanism. It was known that the blood of horseshoe crabs has the ability to form a quick clot at the site of injury in response to the presence of foreign bacteria, but Bang observed an out-of-control clotting reaction that solidified nearly the entire circulatory system into a gel. He cultured a Gram-negative bacterium from the first crab and verified that it provoked the same reaction in other crabs, even when killed. His findings were quietly published in *The Biological Bulletin* and a few years later in *The Bulletin of Johns Hopkins Hospital*, but rather than continuing to pursue this line of research, Bang went back to his previous work on Rous sarcoma virus at the end of the summer.⁷

A decade later, Bang returned to that odd coagulation he found in *Limulus* when a colleague at Hopkins recommended that he work with a young hematology research fellow, Jack Levin, who was at the time

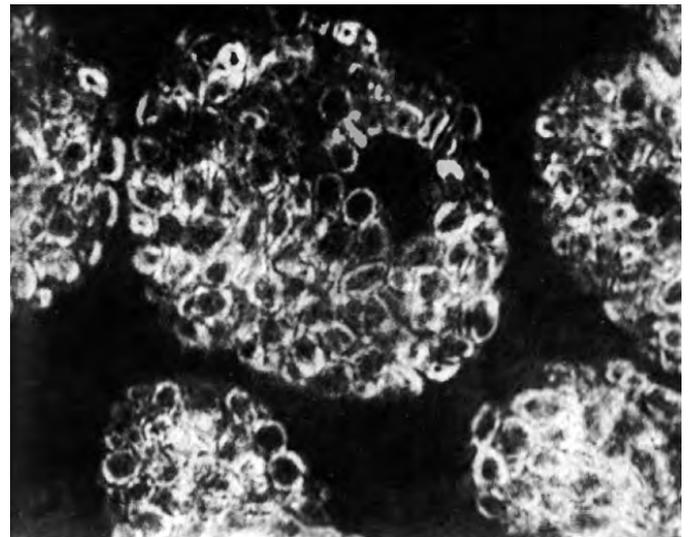
researching how blood clots formed in rabbits in response to bacterial endotoxins. Bang took Levin to the MBL for another summer with the horseshoe crabs.

Levin's Development

At Woods Hole, Levin showed that in order for *Limulus* blood to clot from bacterial exposure, the presence of amebocytes—the only cellular component of the blood—was required. However, his samples of whole blood kept coagulating even in the absence of any known bacteria. He considered the possibility of endotoxin contamination. Levin ran his experiment again using glassware that had been sterilized at a temperature high enough to destroy endotoxins.

When the new samples did not clot, Levin had his “aha moment.” He knew that the blood of the horseshoe crab had to be particularly sensitive to endotoxins.⁸

Further explorations confirmed the endotoxin reaction and narrowed the clotting mechanism down to specific enzymes held by granules within the amebocyte cells. Levin and Bang first published these findings in 1964.⁹ The pair also presented their findings at the 1966 Federation of American Societies for Experimental Biology meeting.¹⁰



Photomicrograph of *Limulus* amebocytes, 3500x
Levin & Bang

The LAL Test

Levin recognized that this discovery had enormous potential as a reliable, sensitive, and rapid test for the presence of endotoxins in pharmaceuticals. In the 1960s, the only way to test a batch of injectable drugs for endotoxin contamination was the rabbit pyrogen test, which required injecting a rabbit with a sample and waiting 4–6 hours to see if it developed a fever.

The *Limulus* amebocyte lysate (LAL) assay that Levin created can detect endotoxins at a concentration of one part per trillion, and in only 45 minutes. Furthermore, the rate of

production of the clot is proportional to the endotoxin's concentration, so the test can indicate to what degree a sample is contaminated.¹¹ Best of all for the horseshoe crabs, the blood can be drawn non-lethally, and they can be released back into the ocean after their donation.

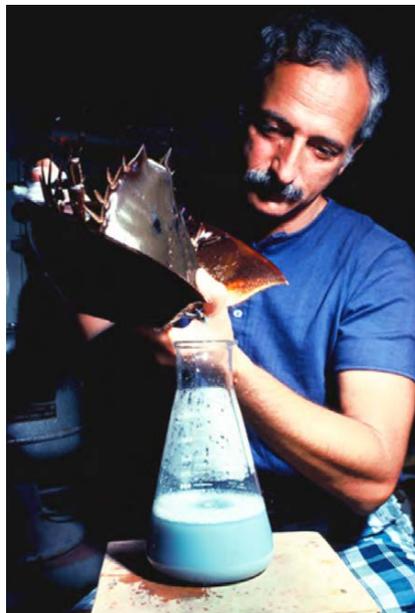
FDA Approval

It was not until 1983 that the LAL was fully approved by the U.S. Food and Drug Administration as a finished product test. Concerns about the sustainability of horseshoe crabs delayed approval for several years as marine biologists debated whether the species could be used responsibly as a natural resource. The potential application of the LAL prompted an increase in research on the behavior and ecology of horseshoe crabs so that scientific advances would “not endanger the elegantly adapted species and bring its long story to an end.”¹²

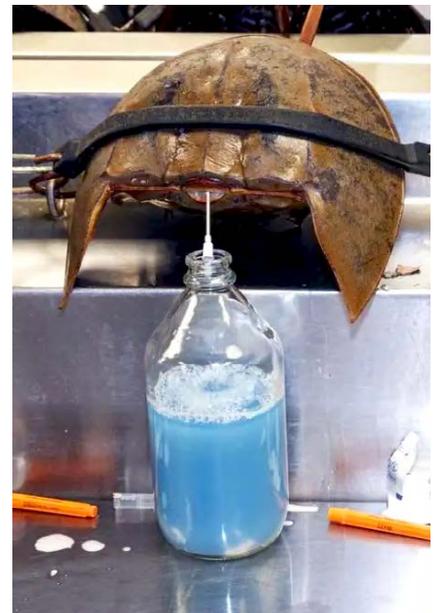
When testing vaccines, LAL is used at multiple steps in the production process to ensure that the containers, stoppers, and ingredients are free of endotoxins before the finished product is tested. LAL is also instrumental in assuring the safety of injectable drugs, implantable medical devices, and IV fluids.¹³

Conservation

Medical use of *Limulus* was not the first impact to the horseshoe crab population. Beginning in the 1850s and continuing into the 1940s, Americans harvested over a million horseshoe crabs per year for bait, fertilizer, and livestock feed. Although there was no baseline population data to compare, this level of predation likely had a



*Jack Levin manually collects Limulus blood at the MBL in 1977.
Marine Biological Laboratory*



*Modern blood extraction from living horseshoe crabs
Shark River Cleanup Coalition*

significant impact on the overall population, prompting wildlife authorities to consider conservation measures. Horseshoe crabs can live close to 20 years and take seven to nine years to reach sexual maturity. When they are taken as they crowd the beaches during a spawn, fewer eggs may be laid, reducing the size of the next generation.¹⁴

Today, around half a million horseshoe crabs are captured for blood collection and returned to their ocean habitat, with a survival rate of 85–90%. Some crabs that are harvested for bait production are bled for the biomedical industry before processing, which has effectively increased the quota of blood available for production of LAL. The Atlantic States Marine Fisheries Commission monitors the estimated population and recommends limits on capture and harvest each year, and as of 2019,



*Horseshoe crab harvest for fertilizer, 1928
Delaware Public Archives*

has determined that biomedical use has had no impact on the population.¹⁵

Bang's Legacy

Fred Bang, who made the original discovery that led to the LAL assay, died in 1981. Five years later, his widow, Betsy Bang, bequeathed \$50,000 to AAI to establish the Frederick B. Bang Scholarships. This gift provided for “support of scholarly research in the science of marine invertebrate immunology” through awards of up to \$10,000 per year through 1994, when the fund was exhausted.¹⁶

The LAL assay is still used today in clinical settings and to test drugs and vaccines for the presence of dangerous endotoxins before they are released. It has been an

essential part of making sure that the COVID-19 vaccines are free from contamination. One manufacturer estimated that one day's production of LAL at all U.S. facilities would be enough to test five billion doses of COVID-19 vaccine.¹⁷

Bang could not have guessed the impact his discovery would have on the world when he first noticed the odd clotting in the blood of the horseshoe crab. Although he and Levin never received a major scientific award for their work, they were finally recognized in 2019 with the Golden Goose Award by the American Association for the Advancement of Science, a prize designed to encourage basic science funding by highlighting “seemingly obscure studies that have led to major breakthroughs and resulted in significant societal impact.”¹⁸

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Nobel Prize medal
NIH

The Nobel Laureates of AAI

The story of the Nobel Prizes begins in 1850 in the Paris laboratory of the Italian chemist Ascanio Sobrero, where a young Alfred Nobel first encountered nitroglycerine. Sobrero had discovered the unstable and highly explosive chemical three years earlier and Nobel, against Sobrero's advice, sought to find commercial uses for it. Eventually, after causing an accidental explosion that killed his younger brother, Nobel developed a stable, solid compound of nitroglycerine that he called dynamite. His invention transformed mining and engineering, allowing for feats of construction that would have been impossible without such explosive power.



Dynamite blast during excavation of Panama Canal, ca 1904–1914
Digital Library of the Caribbean

Of course, dynamite also had military applications. Nobel had somewhat naively believed that dynamite was so frighteningly powerful that it would make war obsolete. According to his biographer, the truth was driven home in 1888 when Nobel opened a newspaper and read his own obituary, which called him a “merchant of death.”



Alfred Nobel
Library of Congress

The newspaper writer had confused Alfred Nobel with his brother Ludvig, who had in fact died. Not wanting to be remembered as a war profiteer, he decided to use his wealth for good and thus established the Nobel Prizes to recognize “those who have conferred the greatest benefit to humankind.”¹ Unfortunately, no copy of the alleged obituary has ever been located. Nobel never spoke publicly about the actual inspiration behind the prizes.²

After a long career of invention and engineering, Nobel stipulated in his will that 94 percent of his estate would be invested, with the interest funding the prizes. The initial five categories of achievement were physics, chemistry, physiology or medicine, literature, and peace, and were to be awarded with “no consideration...given to nationality.”³ The arrangement angered his family members, who expected to inherit the sizable fortune, as well as many

HISTORY

of his fellow Scandinavians, who were incensed that awardees from other countries would be considered.⁴

Immunology Recognized

Alfred Nobel died in 1896, and the first Nobel Prizes were awarded in 1901. The very first prize in Physiology or Medicine was awarded to Emil von Behring for his work on serum therapy, which had laid the foundation for the early field of immunology. Future prizes would confirm the centrality of immunological research to the larger biomedical field and to public health in the world at large.

Since 1901, Nobel Prizes have been awarded to 27 AAI members for their innovation and achievements in immunology and related disciplines. They range from early 20th century discoveries elucidating fundamental properties of blood to more recent breakthroughs that have led to better understanding and successful clinical



Emil von Behring's Nobel Prize Certificate
Wikimedia Commons

treatments of both ancient scourges like cancer and novel diseases such as COVID-19. Four laureates spanning nearly 80 years of the association have served as AAI Presidents: Karl Landsteiner (AAI 1922, president 1927–28), John F. Enders (AAI 1936, president 1952–53), Baruj Benacerraf (1957, president 1973–74), and James P. Allison (AAI 1978, president 2001–02). Immunologists continue to make important scientific advances and discoveries with broad-reaching possibilities, offering the potential every year for another AAI member to be given this honor. No more than 15 years have ever elapsed between instances of the prize being bestowed on an immunologist, and on two occasions AAI members have been honored in successive years.

The Nobel laureates of AAI hail from all over the world, with the prize going to scientists from Australia, Belgium, France, Germany, Japan, Switzerland, and the United Kingdom, as well as the United States. Several laureates are immigrants to the United States, including Landsteiner, born in Austria; Benacerraf, who immigrated from Venezuela; and Salvador Luria, who left fascist Italy in 1938.

Here we present brief profiles of some of the AAI Nobel laureates, representing a selection of the immunological developments to be recognized since 1919. In a previous article, the work of Enders, Thomas Weller (AAI 1943), and Frederick Robbins (AAI 1952) on culturing the poliovirus was featured.⁵ Full profiles of all laureates are available on the AAI website at www.aai.org/Nobel.

Bordet (1919)

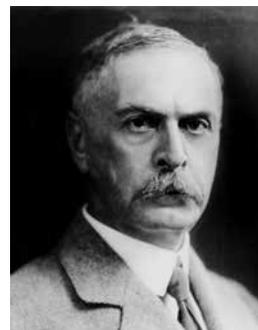


Jules Bordet
AAI Archives

Jules Bordet (AAI 1960) was the first AAI member to be awarded the Nobel Prize in Physiology or Medicine “for his discoveries relating to immunity.” His peers had previously nominated Bordet in 1902 along with Emile Roux (who never won the prize himself), and Bordet had received additional nominations each year since 1908. Although he won the 1919 prize, an obscure rule in Nobel’s will meant that he would not receive it until the next year. Bordet did not even know he had won until 1920, when the announcement was made while he was traveling in the United States.⁶

In the award ceremony, the Nobel committee recognized the critical importance of immunology as a field as well as Bordet’s specific contributions, particularly his discovery of complement and his development of complement fixation tests that led to a wide range of further discoveries and diagnostics.⁷

Landsteiner (1930)



Karl Landsteiner
AAI Archives

Karl Landsteiner was the first Nobel Laureate to be an active AAI member at the time of the award, which was given in 1930 “for his discovery of human blood groups.” Although Landsteiner had made his initial findings in 1900, the importance of blood groups was not widely realized until 1910. When *The Journal of Immunology* was founded in 1916, Landsteiner’s impact was obvious in the many studies on

blood groupings that were published in the early volumes. The Nobel committee also acknowledged the legal and forensic doorways that blood typing opened, as now blood samples could be used to rule out crime suspects or potential fathers in a paternity dispute.⁸

Stanley (1946)

Wendell Stanley (AAI 1957) holds the distinction of being the only member of AAI to receive the Nobel Prize in Chemistry, which he shared with John Howard Northrop



Wendell Stanley
AAI Archives

in 1946 “for their preparation of enzymes and virus proteins in a pure form.” Prior to Stanley’s research, the physical nature of viruses was unknown. In the 1930s, he managed to crystalize the tobacco mosaic virus, ending the debate and demonstrating that viruses were particles too small to be filtered or seen by the equipment of the day. Further experimentation showed that viruses were composed of

proteins and RNA, which explained how they are replicated. Stanley’s work transformed the field of virology and was a key step in understanding how to produce immunity to viruses.⁹ Later in his career, Stanley turned his attention to cancer, and announced to a skeptical audience at the 1956 National Cancer Conference: “I believe the time has come when we should assume that viruses are responsible for most, if not all, kinds of cancer.”¹⁰

Edelman and Porter (1972)



Gerald Edelman
AAI Archives

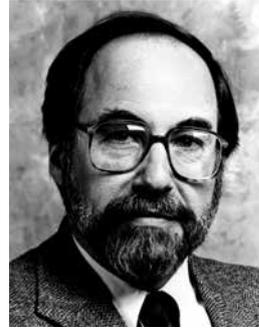


Rodney Porter
AAI Archives

Gerald Edelman (AAI 1970) and Rodney Porter (AAI 1973) shared the 1972 Nobel Prize in Physiology or Medicine “for their discoveries concerning the chemical structure of antibodies.” Working independently in 1959, both scientists had broken antibody molecules into fragments to see how their properties would be altered. Porter split an antibody with the enzyme papain, and found that it divided into three fragments, two of which retained the ability to combine with its antigen. Edelman separated the antibody into several chains with no such capability. The well-known Y-shaped model of the antibody comes from Porter’s explanation that the chains Edelman found were arranged into branches, and it is the specific arrangement of elements that enables reactivity to antigens.

The Nobel Committee’s press release for the award contained a rather back-handed compliment to the field: when Edelman and Porter “provided a clear picture of the structure and mode of action of a group of biologically particularly important substances... they laid a firm foundation for truly rational research, something that was previously largely lacking in immunology.”¹¹

Baltimore (1975)



David Baltimore
AAI Archives

David Baltimore (AAI 1984) received the 1975 Nobel Prize for Physiology or Medicine, sharing it with Renato Dulbecco and Howard Temin “for their discoveries concerning the interaction of tumor viruses and the genetic material of the cell.” In 1970, following Dulbecco’s discovery that genetic material from DNA tumor viruses actually remains in and is replicated by host cells, Baltimore and Temin both found an enzyme in RNA tumor viruses that could form DNA from an RNA template. This enzyme became known as reverse transcriptase.¹²

The discovery of reverse transcriptase allowed for the development of several new microbiological advances and technologies, including enrichment of cellular mRNA, molecular cloning, and the discovery of oncogenes.¹³

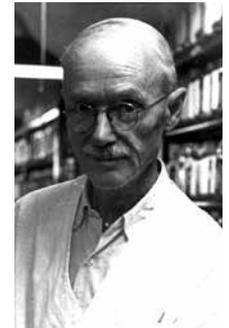
Benacerraf, Dausset, and Snell (1980)



Baruj Benacerraf
AAI Archives



Jean Dausset
AAI Archives



George Snell
Southwest Harbor Public Library

Baruj Benacerraf, Jean Dausset (AAI 1975), and George Snell were awarded the 1980 Nobel Prize in Physiology or Medicine “for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions.” Independently, the three scientists made key contributions that built on one another: Snell discovered the role of the histocompatibility gene H-2 in transplant rejection; Dausset showed the existence of H-2 in humans; and Benacerraf discovered the immune response (*Ir*) genes.¹⁴ Together, these findings elucidated the major histocompatibility complex (MHC), which is a component of the immune system of all vertebrates.¹⁵

Jerne, Kohler, and Milstein (1984)

Niels Jerne (AAI 1965) won the 1984 Nobel Prize in Physiology or Medicine “for theories concerning the specificity in development and control of the immune system,” sharing the prize with Georges Kohler (AAI 1985) and César Milstein (AAI 1979), who were honored for “the discovery of the principle for production of monoclonal



Niels Jerne
AAI Archives



Georges Kohler
AAI Archives



César Milstein
AAI Archives

antibodies.” Jerne “outlined the development of modern immunology” in three crucial theories: (1) that specific antibody response is predetermined in the womb; (2) that lymphocytes “learn” to distinguish self from non-self in the thymus where they are exposed to histocompatibility antigens; and (3) that antibodies can stimulate the production of anti-antibodies in a cascading manner that finds equilibrium under normal conditions. The third of these, known as the “Network Theory,” provided the foundation for numerous translational applications ranging from allergy and infectious disease treatment to transplantation and autoimmune disorder management.¹⁶

Kohler and Milstein developed the hybridoma technique for producing monoclonal antibodies by fusing antigen-immunized cells to immortalized myeloma cells, effectively creating a factory for antigen-specific antibodies. Without their innovation, we would not have had one of the most important treatments for immunocompromised and immunosuppressed people during the COVID-19 pandemic.

Doherty and Zinkernagel (1996)



Peter Doherty
AAI Archives



Rolf Zinkernagel
AAI Archives

The 1996 Nobel Prize in Physiology or Medicine went to Peter Doherty (AAI 1976) and Rolf Zinkernagel (AAI 1976, DFAAI 2019) “for their discoveries concerning the specificity of the cell mediated immune defense.” Their research showed that when a cell has been infected by a virus, a lymphocyte must recognize two factors in that cell before killing it: MHC antigens and the virus. This simultaneous recognition of and distinction between both self and non-self factors is one of the checks that limits the

cellular immune system from activating inappropriately.¹⁷

Understanding that the strongest T cell responses are elicited by “altered self” targets led to advances in transplantation, vaccine development, and treatment of autoimmune and infectious diseases.

Prusiner (1997)



Stanley Prusiner
AAI Archives

Stanley Prusiner (AAI 1981) received the 1997 Nobel Prize in Physiology or Medicine “for his discovery of Prions—a new biological principle of infection.” When one of his patients died of Creutzfeldt-Jakob Disease (CJD), Prusiner decided to identify the mysterious infectious agent that was neither bacterium nor virus. Knowing that the CJD and similar diseases such as kuru and scrapie were transmitted

via brain tissue, he eventually produced from hamster brains a preparation containing the agent: a single protein he named a proteinaceous infectious particle, or “prion” for short. Prusiner’s 1982 discovery came just in time to help inform the management of the “mad cow disease” epidemic of bovine spongiform encephalitis (BSE) in the United Kingdom.¹⁸

Allison and Honjo (2018)



James Allison
AAI Archives



Tasuku Honjo
Nobel Committee

The most recent Nobel laureates in AAI are James Allison and Tasuku Honjo (AAI 1988), who won the 2018 Nobel Prize in Physiology or Medicine “for their discovery of cancer therapy by inhibition of negative immune regulation.” Curing cancer has always been one of the most sought-after goals in medical science, and the immunotherapy that Allison and Honjo made possible is one of the most promising developments in history. Working with the T cell protein CTLA-4, understood to act as a “brake” on the immune system, Allison discovered a way of “releasing the brake” and letting the T cells attack tumor cells when they otherwise would not. Honjo identified a second brake protein that worked differently but also proved effective in attacking cancer.¹⁹

Allison and Honjo certainly will not be the last AAI members to be recognized by the Nobel Committee, as the field continues to produce important research with wide applications in both basic and translational realms.

Other Nominations

Although the Nobel nominations are sealed for 50 years, the available records show that many other AAI members have been recommended for the award, some several times. Among the presidents of AAI, John Kolmer (AAI 1913, president 1917–18), Hans Zinsser (AAI 1917, president 1919–20), Rufus Cole (AAI 1917, president 1920–21), Frederick Novy (AAI 1920, president 1924–25), Ludwig Hektoen (AAI 1919, president 1926–27), Karl F. Meyer (AAI 1922, president 1940–41), Thomas Francis Jr. (AAI 1930, president 1949–50), and Colin MacLeod AAI 1937, president 1951–52) were all nominated once. Thomas Rivers (AAI 1921, president 1933–34) received nominations

in two years, and Alphonse Dochez (AAI 1920, president 1931–32) in three. The two past presidents with the most frequent nominations are Michael Heidelberger (AAI 1935, president 1946–47, 1948–49), nominated 18 times between 1937 and 1962, and Oswald T. Avery (AAI 1920, president 1929–30), with 18 between 1932 and 1957.

Nearly all of these nominations were in Physiology or Medicine, but occasionally a member has been nominated for the Chemistry prize as well. Understandably, the Nobel Committee issues the prizes to scientists in a wide range of fields, but hardly a year has gone by that an immunologist has not been considered for the highest honor in science.

For more in-depth profiles of every one of the 27 AAI Nobel laureates, including their background, research, and influences, visit the AAI History site at www.aai.org/Nobel.

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Drafting Doctors: New Generations of Immunologists in Bethesda

Draft lottery for the Vietnam War, 1972
Library of Congress

by Charles Richter, Ph.D., AAI assistant historian, and John Emrich, Ph.D., AAI historian and archivist

Since its founding, many members of the American Association of Immunologists (AAI) have had close ties to the National Institutes of Health (NIH) and its precursor agencies. Located just outside of Washington, DC, NIH has funded and trained countless immunologists. Two generations of AAI members joined its staff and leadership during periods of NIH expansion, thanks in part to a Cold War era policy that attracted young physicians to the Maryland suburb of Bethesda.

A Wartime Need

During the First and Second World Wars, the rapidly expanding U.S. Armed Forces needed physicians to treat sick and injured soldiers on the frontlines and at bases back home, as well as to conduct war-related research. AAI members responded during both wars by volunteering for military service or carrying out important disease research on the homefront.¹

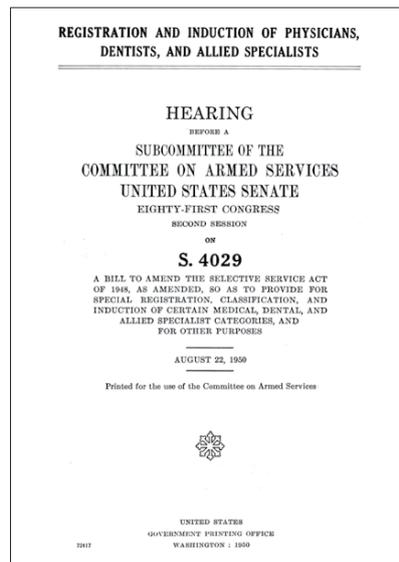
Within a decade of the end of the Second World War, Cold War tensions between the United States and the Soviet Union were felt around the world. In 1948, to maintain readiness during this new

era, the U.S. government reorganized the Selective Service System, the agency responsible for furnishing able men for common defense and national emergency, including a military draft. The legislation also contained provisions for drafting physicians in peacetime. Less than five years later, President Harry S. Truman signed into law an act establishing the male-only Doctor Draft, which changed the trajectory of many physicians and future AAI members.

From 1953 to 1973, countless young doctors satisfied their two-year military obligations as staff physicians or researchers at military installations or the frontlines of the Korean and Vietnam Wars. Additionally, more than 4,000 newly minted doctors fulfilled their service by spending at least two years as associates at the NIH, gaining invaluable clinical and research experience. Of these, more than 160 would go on to become members and leaders of AAI.

The Doctor Draft and Associate Training Program

John L. Fahey (AAI '64) first heard about the new Associate Training



Doctor Draft legislation, 1950
U.S. Government Printing Office

Program (ATP) at the NIH Clinical Center in the spring of 1950, when he was a student at Harvard Medical School. He viewed the program, which was set to begin in 1953, as an excellent career opportunity.² Little did he know that by the time he was accepted, it would also be an alternative to military conscription.

When North Korean forces suddenly invaded South Korea on June 25, 1950, Congress and President Truman quickly responded by reactivating the general military draft and launching a new Doctor Draft. Over the next six years, more than 30,000 physicians, dentists, and veterinarians would be drafted to serve both overseas and in stateside bases.³



Surgery in the 8209th MASH unit in Korea, 20 miles from frontlines, 1952
National Archives

Under the new law, all doctors up to the age of 50 would be required to serve in a branch of the armed forces or in the Public Health Service (PHS), which includes the NIH (see sidebar on page 67). Fahey later described how the NIH program benefited new doctors: “A commission in the PHS was regarded as equivalent to military service. By joining the PHS at the NIH, I was able to help the new national effort to develop a Medical Research Center and continue my career development in biomedical research without an interruption for military service.”⁴ Fahey and the rest of that first group of clinical associates arrived at the NIH on the opening day of the Clinical Center, July 2, 1953, just weeks before the end of the Korean War.

The Berry Plan

After the Korean War, Frank Berry, the new Assistant Secretary of Defense for Health and Medical, came into office with a plan that he hoped would both provide sufficient military personnel for the Cold War military and satisfy the concerns of hospitals, medical schools, and physicians’ associations. Under the “Berry Plan,” new doctors had more flexibility as to when they began their service: they could choose to join a branch of the armed forces or PHS immediately following their internship, after one year of residency, or after a full

residency in the specialty of their choice. Although their preference of service branch had to be stated in their fourth year of medical school, graduates were not guaranteed to receive their first choice.⁵ Those who entered the PHS were commissioned at the rank of senior assistant surgeon, equivalent to lieutenant in the Navy.⁶

The Doctor Draft continued into peacetime following the Korean Armistice Agreement, according to Berry’s plan. For some doctors, it provided their first experience with immunology, which for many of them became a lifetime pursuit. A number of these immunologists became pioneers in the field and future AAI leaders.

Military Service

Even for those who did not become NIH associates, it was still possible to end up in Washington, DC. K. Frank Austen (AAI ’62, resident 1977–78) was the only one out of his cohort of 12 interns at Massachusetts General Hospital who did not apply to the ATP in

1956, but joined the Army instead. He recalled: “When I completed my basic training in Fort Sam Houston in Texas, and the nice sergeant who was doing our assignments looked and saw that I had three papers in the *New England Journal of Medicine*, the sergeant decided I might have potential as a scientist, and rather than assign me to overseas (I was assuming it would be South Korea), sent me to the Walter Reed Army Institute of Research, where, in turn, they assigned me to the one immunologist [Elmer L. Becker (AAI ’52)] that the Army had at a time when the NIH did not have an immunology program.”⁷



Frank B. Berry, Asst. Secretary of Defense for Health
National Library of Medicine



Walter Reed General Hospital
National Library of Medicine



For an in-depth look at how the Doctor Draft affected the career arc of an AAI member, see our story on Frank Fitch (AAI 1961, president 1992–93) and his years as an Air Force physician in the 1950s in the January/February 2018 issue of the *AAI Newsletter*.

PHS and NIH

Entrants into the NIH associate program were in one of three categories: clinical associate (CA), research associate (RA), or staff associate (SA). When the Clinical Center opened in 1953, all associates were CAs. RAs were added in 1957, and the first SAs joined in 1960.

CAs had primarily clinical responsibilities caring for NIH patients, while RAs, having no obligations in the clinic, were each assigned to an institute and laboratory that fit his research interests. SAs gained experience in both basic research and research administration. Associates in all categories would generally spend two years at NIH, except for those placed in the National Institute of Allergy and Infectious Diseases (NIAID), which had three-year clinical associateships consisting of one year in the clinic and two in the laboratory. In those early years, though, CAs in all institutes had the chance to perform a great deal of basic research, as the Clinical Center had not yet built up the robust referral system it has today.⁸

The vast majority of future AAI members in the ATP worked in three institutes: the National Cancer Institute (NCI), NIAID, and what was then known as the National Institute of Arthritis and Metabolic Diseases (now the National Institute of Arthritis and Musculoskeletal and Skin Diseases or NIAMS).



The Clinical Center at NIH, 1960
National Institutes of Health

Being accepted into the new associate program at NIH seemed like winning a scientific jackpot. Thomas A. Waldmann (AAI '71) arrived at NCI as a CA in 1956, having had almost no laboratory research

experience. He enjoyed learning “from the corridors” during his walks to lunch with various colleagues. Many associates were in a similar situation. As Henry Metzger (AAI '65, AAI president 1991–92) remembered, when he was an RA in 1959 “...they also had some courses, lectures...because many of us didn't have all that much basic science training when we came.”

In the early 1960s, according to William E. Paul (AAI '67, president 1986–87), who was a CA at NCI from 1962 to 1964, “...it wasn't Vietnam, it wasn't Korea, but people would still prefer not to be in the service if they could avoid it....If you were fortunate enough to get a position at NIH...that was an entrée to science, not just for me, but for a whole generation.”

Matthew D. Scharff (AAI '64) received encouragement from New York University Medical School to apply to the ATP as an alternative to the draft. The NIH option within the PHS was particularly attractive to Scharff, who was an RA from 1961 to 1963: “Instead of going off and being a physician in

Origins of Military Service at the NIH

The origins of the U.S. Public Health Service (PHS) date to 1798, when President John Adams signed the first federal health law, the Act for the Relief of Sick and Disabled Seamen, which created a series of locally controlled marine hospitals on major U.S. waterways. In 1870, the hospitals were reorganized to be federally controlled and renamed the Marine Hospital Service (MHS). In 1887, the MHS built a one-room Hygienic Laboratory to study cholera at the Marine Hospital at Stapleton on Staten Island. Congress established the Commissioned Corps in 1889 to formalize the military model that had been used by the MHS as it evolved into a force to fight outbreaks of disease. Officers in the Commissioned Corps held ranks and paygrades as in the Army and Navy. In 1912, the name of the MHS was changed to the Public Health Service to reflect the broader responsibilities of the service, and in 1917, President Woodrow Wilson issued an executive order constituting the PHS as part of the U.S. military. In 1930, the Hygienic Laboratory was renamed the National Institute of Health (NIH).

1940: New NIH campus in Bethesda dedicated

1943: Full military benefits authorized for commissioned officers in the PHS

1944: Public Health Service Act allows for nurses, scientists, and other medical personnel in Commissioned Corps

1948: Selective Service Act of 1948 establishes modern system of conscription in wartime

1950: Korean War begins on June 25 when North Korean forces invade South Korea

1950: First draft call for doctors and dentists to support fighting in Korea

1952: Doctor Draft Law mandates service in the military or PHS for all physicians up to age 50

1953: The NIH Associate Training Program begins; the first Clinical Associates start their terms

1957: NIH Associate Training Program adds Research Associates

1964: The Gulf of Tonkin incident prompts U.S. deployment of regular combat troops.

1969: Beginning of general draft lottery

1973: Paris Peace Accords are signed, ending U.S. military activity in Vietnam

1975: Fall of Saigon; complete U.S. withdrawal of troops from Vietnam

the Aleutian Islands or some place in some clinic, you could go to the NIH and essentially be a postdoctoral fellow.” Even though the United States was not currently engaged in a war, the NIH offered a much more interesting way to serve than, as Metzger put it, “doing physicals at some army base.”

The NIH itself told prospective applicants that it offered “unusual opportunities” unlike those found elsewhere.⁹ Getting into the program, however, was not easy; in 1962, the ATP received 1,200 applications to the program, and accepted 123 new associates.¹⁰ This was a large increase over the 85 acceptances from 500 applications the previous year.

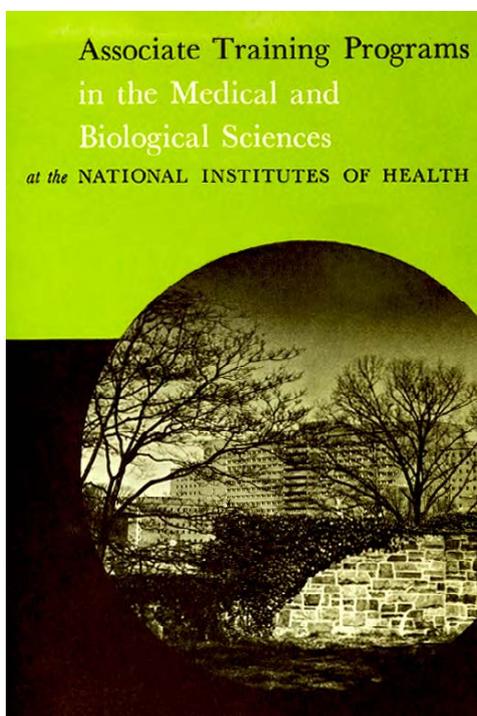
The Vietnam War Era

The number of associates at the NIH steadily increased through the 1960s and through the duration of the Vietnam War (1965–75). Even before the general draft lottery was instituted in 1969, new physicians were subject to the Doctor Draft and deployment to Vietnam. As American involvement in the war ramped up after the Gulf of Tonkin Resolution in 1964, an ATP position at the NIH looked increasingly desirable, both to avoid the hazards of war and as a stepping stone to scientific opportunity. Robert R. Rich (AAI '73, EIC 2003–08) was not unique among his generation when it came to serving as a military doctor. “I could have gone to Vietnam,” he recalled, “but I decided the NIH was probably more to my liking for that period of service.”¹¹



Thousands of doctors were needed to support the 8.7 million soldiers who served in the Vietnam War
National Archives

Prospective associates had to apply during their final year of medical school, and most of those who accepted chose to complete their medical residency before beginning their NIH training. With the number of applicants skyrocketing, the deadline for the program had to be moved up from September to May in 1965, and then to April in 1968. A student hoping to start as an associate at the NIH in July 1968, for example, would have to have his application



Associate Training Program Catalog, 1965
National Institutes of Health

completed by early May of 1966.¹² The schools that supplied the most future AAI members to the ATP included Harvard Medical School (24), Columbia University College of Physicians and Surgeons (13), New York University School of Medicine (12), and Johns Hopkins University School of Medicine (10).

The war drove Ethan M. Shevach (AAI '73, EIC 1987–92) to apply to the ATP and pursue a career in medical research. As he explained later, “The big career decision in 1967 when I graduated medical school was the Vietnam War. That was a big influence on one’s career. And as a physician, to be honest, it didn’t appeal to me to go to Vietnam. I was drafted by the army, as every male physician was drafted in those days, and was pretty likely going to spend a year as a general medical officer in Vietnam. The other alternative was to embark on a career in medical

research and come to the NIH.” Shevach had to plan his honeymoon so that he could quickly get to Bethesda if he got the call for an interview.¹³ His eventual placement at NIAID led to a life-long career at that Institute.¹⁴

Irving Weissman (AAI '71, AAI president 1984–85) was an activist against the war in Vietnam while attending Stanford Medical School in the early 1960s. He was interested in joining the ATP, but after organizing a petition stating that physicians could not ethically serve under the military code, Weissman reported two consequences: “One, I got my draft notice early, and two, when I called to go to the NIH, they said, “You’ve been blackballed.” So I couldn’t go to NIH.” Only a swift appointment at Stanford kept Weissman from being drafted.¹⁵

As the Clinical Center matured and benefited from the growing influx of bright young minds, the associates enjoyed a remarkably collegial environment. John I. Gallin (AAI '75) described how, as a clinical associate in the early 1970s, he was “adopted by all the senior staff” and “felt totally free to interact with all of them.” At least 39 AAI members were ATP associates in the early years from 1953 to 1965, and a few, like Waldmann and Metzger, had long careers at NIH, where they became mentors to many ATP associates and future AAI members. William Paul became mentor to Charles A. Janeway Jr. (AAI '74, AAI president 1997–98) in 1970.¹⁶ At any given time from 1967 to 1973, there were never fewer than 36 future AAI members in the ATP, and at times as many as 50.

ATP and the “Yellow Berets”

Before long, the Vietnam-era physicians who fulfilled their military obligation through service at NIH acquired the nickname of “yellow berets.” While the term was initially

Anthony Fauci as an NIH Clinical Associate
The NIH Record



used as an insult against those who avoided the war, it was appropriated as an ironic badge of honor by many of the associates. Janeway considered the “yellow beret” moniker a “joking name for the group that came of age at the end of the 1960s and did not want to serve in the Army in Vietnam in what [they] regarded as an unjust war.” Particularly as competition for spots at NIH grew fiercer, the proud few who were selected had been at the top of their classes in medical school.

Not everyone appreciated the “yellow beret” label; Anthony Fauci (AAI '73), who was a CA from 1968 to 1970, at the height of the war, argued that it gave the false impression that the associates were “afraid of going to war.” On the contrary, he explained, “I always felt that if indeed it came to that, that I would go. I was not philosophically in favor from the political standpoint of the real rationale of why we were there. As long as American soldiers were going there and getting killed and getting maimed, as a physician I felt if I had to go, I would gladly do my part to try to help them. I did not have a problem going to Vietnam even though I had a problem with the war itself.”¹⁷

Metzger, who ran a laboratory in the Arthritis and Rheumatism Branch, in what is now NIAMS,¹⁸ in the late 60s, said of his own RAs’ reasoning for selecting the NIH during the Vietnam War, “I guess it wasn’t something that we discussed because if they were here, in a sense they had accomplished what they wanted to.”¹⁹ When Metzger interviewed prospective associates, he did not inquire as to their reasons beyond scientific interest. The NIH

campus was a welcoming place for those who were not in favor of the war; beginning in 1969, the National Institute of Mental Health (NIMH) had organized the NIH-NIMH Vietnam Moratorium Committee, which sponsored an annual rally onsite to protest the ongoing war.²⁰

Through the war years, total enrollment in the program steadily rose from 177 associates in all fields in 1966 to a high of 224 in 1973, when both the general draft lottery and the Doctor Draft ended. After the war, the ATP continued as it had originally been intended, with no connection to conscription.

Shaping the Future

The ATP also had the unintended consequence of limiting opportunities for women scientists at the NIH. Fauci remembered a recruiting major in the Marines visiting his fourth-year class at Cornell Medical School to remind everyone to put in their preferences of service branch—everyone except the two women out of a class of 88.²¹ As only men were subject to the draft, only men were eligible to be selected as associates at the NIH. For some NIH investigators, hiring a woman outside of the ATP meant sending a man into war, so they would only hire men as associates.²² Associates at NIH were much more likely than their peers to become full professors, department chairs, and deans, as well as to receive major science awards and memberships in honorary societies.²³ Thus, the unofficial male-only policy denied women an equal chance for advancement at a time

when they made up a small, but growing, percentage of young physician-scientists.

The research performed by Vietnam-era AAI members during their time in the ATP produced long-lasting and widely used methods, basic science, and clinically relevant papers published in *The JI*. Several highly cited manuscripts provided descriptions of lymphokines and growth factors, laying groundwork for the ongoing study of cytokines and chemokines. The two most-cited articles both described assays for chemotactic factors, one for granulocytes and the other for agranulocytes. The function of immunosuppressive cells was discovered in the early 1970s, and *The JI* published a number of papers concerning suppressor cells, mostly T cells—and one on suppressive macrophages, which has laid the groundwork for today's research in regulatory T cells, myeloid-derived suppressor cells, and more recently regulatory B cells.

For the associates, the NIH became such an attractive place to conduct research that many took the opportunity to continue their careers there far beyond the two or three years of the associateship, creating a hub for immunology research and training. Former associates have been instrumental in many major developments: long after

they were associates, Waldmann and Paul made the NIH an important center for interleukin research; Gallin has used immunotherapy and gene therapy to treat chronic granulomatous disease and led the Clinical Center from 1994 to 2017; and Fauci became a pioneer in AIDS research, headed NIAID from 1984 to 2022, and also led the nation's response to the COVID-19 pandemic.²⁴

The legacy of the Doctor Draft endures to this day. Many of those who participated in the Berry Plan remained in Bethesda and directed the future of the NIH. A cohort of scientists who were given a unique opportunity became leaders and mentors, shaping federal science policy and training new generations of immunologists and future innovators in the field.

In 2013, the AAI Office of History and Archives launched the Oral History Project, which to date has produced video interviews of 49 past AAI presidents and distinguished AAI award recipients, a few of whom are featured in this article. To view one or all the oral histories, visit <http://aaai.org/ohp>.

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SCANDAL! AT THE FDA

WASHINGTON, DC, 1960 — Henry Welch (AAI 1950), the chief of the Division of Antibiotics at the Food and Drug Administration (FDA), has resigned in the face of allegations of corruption. Welch used his position at the FDA to help establish two for-profit journals supported by pharmaceutical advertisements. Although he claimed to receive only “an honorarium” as editor of those journals, it turned out that the honoraria amounted to more than \$250,000 over seven years—about twice his FDA salary. His resignation comes less than a month before his scheduled retirement.



Henry Welch

Welch was one of the first AAI members at the FDA. As director of the Division of Penicillin Control and Immunology, he was responsible for testing every batch of penicillin used by the armed forces in World War II, conducting tests of his own design. After the war, he was appointed director of the Division of Antibiotics, where he had primary responsibility for new drug approval.

FDA FOUNDED TO ENSURE SAFETY

At the turn of the 20th century, there were very few restrictions or standards on producing and selling medicines and drugs. Anyone could sell a “medicine” without disclosing the ingredients, and they could make any claim they wanted regarding its effects. As public awareness of the dangers of this situation was raised by exposés from Upton Sinclair and other journalists, the demand for regulation led to government action.

The proliferation of antitoxins and vaccines in the late 19th century saved many lives, but lax safety standards also caused unnecessary deaths. After a contaminated diphtheria antitoxin killed several St. Louis children in 1901, the Biologics Control Act of 1902 established the first federal biologics regulations, including labeling requirements and unscheduled inspections.

The Pure Food and Drug Act of 1906 outlawed adulteration of drugs and required labeling of active ingredients. This necessitated a robust infrastructure of testing and evaluation. At first, regulatory power was held by the USDA Bureau of Chemistry, but in 1927 the FDA was founded to implement federal standards for food and drugs.

Immunology History Made in the Nation’s Capital



The history exhibit at IMMUNOLOGY2023™

WASHINGTON, DC, 2023 — A record-breaking 4,168 immunologists, exhibitors, and other scientists met in DC this year to present their cutting-edge research, network with colleagues, and attend lectures by some of the world’s leading scientists. The history of immunology in the area was celebrated in both a history exhibit and the return of the newly updated AAI Timeline.

The American Association of Immunologists got its foothold in DC in 1916, when the AAI Council extended honorary memberships to senior scientists at the Army Medical

School, the Naval Medical School, and the Hygienic Laboratory of the Public Health Service—the precursor of the NIH. Membership in the region grew swiftly thanks to the proliferation of immunological research at government, university, and private institutions.

Today, the greater DC–Maryland–Virginia area has one of the largest concentrations of AAI members in the country, and many more immunologists have temporarily called the region home while they completed governmental fellowships and training.

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PIG-TO-HUMAN HEART

Editor:

John Emrich, Ph.D.

Chief Correspondent:

Charles Richter, Ph.D.



TOP SECRET RESEARCH BY AAI IMMUNOLOGISTS



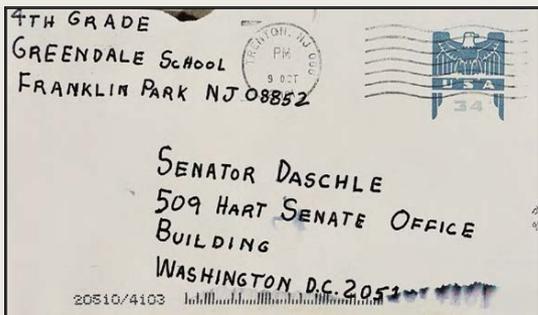
Elvin Kabat (top) and Theodor Rosebury

FREDERICK, MD, 1947 — Elvin A. Kabat (AAI 1943, president 1965–66) and Theodor Rosebury (AAI 1953) have published a lengthy article in *The Journal of Immunology* (*The II*) warning the nation of the dangers of biological weapons. During World War II, the pair of scientists worked under conditions of extreme secrecy at the U.S. Army base to understand which microorganisms could be used against American forces and how to be ready for them. No classified material was used in the article printed in *The II*.

About 45 miles north of DC, Fort Detrick began as a small airfield in 1931, but became critically important during the war as the center of the U.S. armed forces biological weapons division. Although the U.S. military never used biological weapons, there was a constant fear that the Axis powers might. Later, during the Cold War, these concerns extended to the Soviet Union as well.

In 1969, the bioweapons research program at Fort Detrick became the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). All work done at this facility must remain within the confines set by Richard Nixon's 1969 executive order renouncing "the use of lethal biological agents and weapons, and all other methods of biological warfare."

The research at USAMRIID had renewed urgency during the 2001 anthrax attacks, when packages containing active anthrax spores were sent through the mail to reporters, Senators, and Representatives, resulting in 22 infections and five deaths. Immunologists at Fort Detrick were instrumental in developing guidelines for treatment in the case of anthrax exposure, as well as how to address the potential weaponization of many other pathogens.



An anthrax-containing envelope received at the offices of Senator Tom Daschle

Nation's First Immunology Department Founded



The original Johns Hopkins Hospital

BALTIMORE, MD, 1916 — Johns Hopkins University has become the home to the first immunology department in the United States. William H. Welch established the School of Hygiene and Public Health with a grant from the Rockefeller Foundation and decided to include a separate Department of Immunology. Carrol G. Bull (AAI 1917) joined Welch from the Rockefeller Institute for Medical Research in 1917 and that same year produced the first effective antitoxin for gas gangrene, just in time to save many soldiers from a gruesome death in the trenches of World War I.

OPPORTUNITIES INCREASE AT HOWARD UNIVERSITY



Willie Turner

WASHINGTON, DC, 1977 — Willie Turner (AAI 1973) has come to Howard University from the National Cancer Institute and created the Ph.D. program in microbiology. He established programs in immunology as well as in virology, pathogenic microbiology, cell biology, and parasitology. To staff the new department,

Turner recruited 12 minority faculty and required that, upon promotion, they were to take a sabbatical for research. His efforts significantly increased the number of minority scientists in immunology and related fields.

One of the early recruits to the new program was Curla S. Walters (AAI 1973). After receiving her Ph.D. at Georgetown University, Walters taught immunology and microbiology at Howard for 30 years and guided the development of a new integrated medical school curriculum there. In addition to her research and teaching, she coordinated the AAI program for minority high school students as a founding member of the Minority Affairs Committee.

A CHARTER MEMBER OF AAI IN VIRGINIA



Edgar C. L. Miller

RICHMOND, VA, 1913 — Joining the newly formed American Association of Immunologists is Edgar C.L. Miller of the Medical College of Virginia (MCV). Miller, an early researcher of diphtheria antitoxin

and serum sickness, has established the Department of Biochemistry at MCV and pushed for greater funding to develop new treatments for and understanding of diphtheria, tuberculosis, and typhoid fever.

During the influenza pandemic of 1918–19, Miller replaced the director of the emergency hospital in Richmond when he came down with influenza himself. In 1930, Miller became the Directing Librarian of the MCV Library, a position he held for the rest of his career and into retirement as emeritus.

The MCV merged with the Richmond Professional Institute in 1967 to form the Virginia Commonwealth University, which continues to be a major site for immunological research. Longtime VCU immunologist and rheumatologist Shaun Ruddy (AAI 1969) was one of the pioneers of the human complement pathway. With frequent collaborator K. Frank Austen (AAI 1962, president 1977–78), he discovered key components that are now well known to be involved in inflammatory and immune-mediated disorders.



The "Egyptian Building" which originally housed the Medical College of Virginia

Biologics "Lab Technician" Identified After Decades



Hope Hopps, finally identified, pictured with Harry M. Meyer and Paul D. Parkman

BETHESDA, MD, 2018 — This photograph, taken in the 1970s at the Laboratory of Viral Immunology in the NIH Division of Biologics Standards before the unit moved to FDA, was until 2018 captioned "Drs. Harry M. Meyer Jr. (light hair), Paul D. Parkman (dark hair), and a female lab technician...working with rubella antigen in laboratory setting." A researcher at the National Library of Medicine was able to identify the "female lab technician" as Hope E. Hopps (AAI 1958), the research partner of Meyer and Parkman (AAI 1966).



Hope Hopps

More than a lab technician, Hopps was a bacteriologist with a master's degree in microbiology with 89 articles and two patents to her credit, including for the rubella blood test. She developed the BCS-1 cell line essential to ensuring the safety of live poliovirus vaccines. With Parkman and Meyer, Hopps developed the vaccine for rubella, but is rarely credited with the discovery.

Throughout her long career at the FDA, Hopps supported many young scientists and worked as a consultant for the FDA after retirement.

PANDEMIC AVERTED



Maurice Hilleman in his lab at Walter Reed Army Institute of Research

WASHINGTON, DC, 1957 — Maurice R. Hilleman (AAI 1949), chief of the Department of Respiratory Disease at Walter Reed Army Institute of Research, has averted a potential pandemic. In April 1957, Hilleman noticed an article in the *New York Times* about an epidemic of influenza that was spreading through Asia and immediately obtained samples to study. As the discoverer of the “drift and shift” mechanism that produces new strains of virus, he knew that a targeted vaccine had to be produced extremely quickly to avert another influenza pandemic.

Once he identified the strain, Hilleman pressed military and public health leaders to recognize the danger. His campaign led to the production of 40 million doses of a vaccine tailored to the epidemic strain in just a few months. Hilleman would go on to create dozens of vaccines, eight of which are still in current vaccine schedules, and save millions of lives each year.

USDA Enables First Pig-to-Human Heart

BALTIMORE, MD, 2022 — At the University of Maryland School of Medicine, a genetically modified pig’s heart has been successfully transplanted into a human for the first time. This novel operation was made possible in part through the work of immunologist Joan K. Lunney (AAI 1980) and others at the USDA.

Lunney has been working with pigs at the USDA’s Agricultural Research Service (ARS) in Beltsville, MD, since the 1980s and has discovered novel immune mechanisms that help swine resist the common zoonotic foodborne parasites *Trichinella spiralis* and *Toxoplasma gondii*.

Another major project from the Diet, Genomics and Immunology Laboratory at the USDA is the Porcine Translational Research Database, the largest manually curated database for any veterinary species. For 17 years, the database has facilitated the use of pig models for many human diseases as well as elucidating zoonotic transfer of the next potential pandemic viruses.



Joan K. Lunney caring for porcine colleagues

From the History Archives: Marion Morris

“I have always had interesting jobs. I didn’t think they looked like anything on paper, but I was never bored.” — Marion Morris

(above) Washington University School of Medicine, 1926; (right) Marion Morris, 1919

The AAI History Archives are wide ranging and full of hidden gems. Recently, the AAI history staff discovered three photographs of an unidentified female member that seemed to represent the span of her adult life. These turned out to be of Marion C. Morris (AAI 1936), a long-time and very involved AAI member. While not famous for her research, her career arc that spanned much of the 20th century demonstrated the diverse opportunities available to immunologists.

Using documents discovered scattered across many different archives, AAI historians were able to reconstruct Dr. Morris’s career and part of her web of scientific connections, but not much about obstacles she undoubtedly faced as a woman in science. She did not speak about these issues in the one published interview she gave. Her career, research, and dedication to immunology, however, did not go unnoticed: the first AAI executive director remarked to her niece in 1988 that Morris “became one of the distinguished ladies in immunologic science.”¹

Born in Holyoke, MA, in 1902, Morris was six years old when her father unexpectedly passed away. The oldest of her four siblings, she was thrust into a new world of responsibility, supporting her family. In 1919, Morris graduated high school as valedictorian and made the difficult decision to attend Smith College.² A scholarship helped ease the financial burden on the family. She majored in chemistry and graduated *cum laude* in 1923, along with membership in Phi Beta Kappa—the oldest academic honor society in the U.S.³

Early Career

Following graduation, she began her career in science, although she was not yet in graduate school. She began as a laboratory apprentice at the New York State Department of Health in Albany. Four years later, she moved down the Hudson to New York City for a position as a laboratory assistant at the prestigious Rockefeller Institute for Medical Research (RIMR), which she held from 1927 to 1928.⁴

It is unclear why she decided to leave RIMR, which was a hotbed of immunological research at the time, to pursue graduate studies at Washington University in St. Louis. The director of RIMR, Simon Flexner (AAI 1920), was a member of AAI, as were many RIMR scientists. Several would become AAI presidents within the next decade, including Oswald Avery (AAI 1920, president 1929–30), Alphonse Dochez (AAI 1920, president 1931–32), and Thomas Rivers (AAI 1921, president 1933–34). Morris did, however, depart RIMR at the same time that two institute scientists decamped for appointments at Washington University School of Medicine: Jacques J. Bronfenbrenner (AAI 1920, president 1942–46) accepted the chair of the department of bacteriology and immunology; and Edmund V. Cowdry became professor of cytology in the department of anatomy.⁵

To WashU

Morris enrolled in the graduate program at Washington University in the fall of 1927 and was employed at the medical

school as an experimental bacteriologist in the Department of Ophthalmology. In 1930, her position in the department changed to assistant in experimental bacteriology and immunology, no doubt reflecting her academic research focus. In 1931, she received her M.S. following the acceptance of her thesis, “The interrelationships of the antibody and hypersensitive responses of rabbits to streptococcus and pneumococcus.”

Morris remained enrolled at Washington University to pursue her doctorate and continued working at the medical school. In 1932, she published her first manuscript with Louis A. Julianelle (AAI 1930), associate professor of applied bacteriology and immunology in the Department of Ophthalmology, who had been a researcher at RIMR from 1924 to 1930.⁶ The following year she joined the Trachoma Commission, albeit with the same title, where she could focus the skills she had developed in bacteriology, immunology, and ophthalmology on one disease.

Trachoma

The commission was created at Washington University in October 1930 “for the study of trachoma and allied diseases.” It was directed by Julianelle and supported by a grant from the Commonwealth Fund.⁷ The stated objective of the commission was “to investigate the nature, cause and treatment of trachoma and the differentiation of trachoma from clinically related diseases.” The Trachoma Commission consisted of an interdepartmental model (ophthalmology, bacteriology, immunology, and biochemistry) in the medical school as well as collaboration with the U. S. Trachoma Hospital at Rolla, MO.⁸

Trachoma was not a new disease, having infected humans since before recorded history. It was an infection in the eye that slowly and painfully led to blindness. However by the late 19th century in the United States, it had become, according to the Surgeon General, a “dangerous, contagious, disease.” Though long endemic in what would be known as the “Trachoma Belt,” an area beginning in central and southern Appalachia and extending into the Midwest,⁹

it was trachoma’s appearance among immigrants from Southern and Eastern Europe that brought the attention and focus of federal public health authorities.¹⁰ Unduly punitive immigration restrictions limited trachoma outbreaks on the coasts, but the largest non-immigration reservoir in the Trachoma Belt required a better understanding of the disease to limit transmission and provide better palliative care.

By the 1910s, it was well known among medical and public health officials that, though the causative agent was not yet identified, unhygienic conditions and poor sanitation were spreading the disease, especially among rural families and schools where shared towels, bed linens, and contaminated wash basins were common. The federal government opened the first field trachoma hospital in Kentucky in September 1913. Other trachoma hospitals would soon open in Virginia, West Virginia, Tennessee, North Dakota, Arkansas, Georgia, and Rolla, MO. Hospitals offered rudimentary surgical and sulfa drug treatments, later becoming a hub for field hospitals and clinics that could perform better disease surveillance in rural areas. The clinics, run typically by nurses, also served as the best way to provide health education and training in the Trachoma Belt. By the early 1930s, improvements in sanitation and teaching of better hygiene began to ameliorate conditions. The specific cause, and thus hope for better treatment and/or a cure, remained elusive.¹¹ (To learn more about trachoma, go to aai.org/history/trachoma.)

Morris’s research was focused on determining the causative agent of trachoma. She worked closely with Julianelle and R. Wendell Harrison (AAI 1934), an applied bacteriology and immunology instructor. A Trachoma Research Committee furthered the work of the commission established in the medical school, which was chaired by Julianelle and included Bronfenbrenner, Cowdry, W. McKim Marriott (professor of pediatrics and dean of the medical school), and Lawrence T. Post (assistant professor of clinical ophthalmology).

In 1937, Julianelle, Harrison, and Morris published the summary of their years-long research.¹² Given the technology they had at the time, many of their conclusions were correct; however, they erred in the causative agent of trachoma,



Bringing eye patients to Lexington, KY, 1916



Typical Kentucky mountaineer home c.1930

concluding that “the accumulated evidence suggests that the infectious agent of trachoma is a virus.”¹³ The etiological agent *Chlamydia trachomatis*, or trachoma, was not positively identified until 1957 when T’ang Feifan, Chang (Zhang) Xiaolou, Huang Yuantong, and Wang Keqian from Tong Ren Hospital in China successfully isolated the bacteria in a chicken embryo. The research team further identified that three strains of chlamydia (A, B, and C serotypes) could cause trachoma.¹⁴

Doctorate and Appointment at WashU

While on the commission, Morris was also carrying out her doctoral research under Bronfenbrenner’s mentorship. Though Bronfenbrenner was nearly a decade into his bacteriophage research, Morris was free to continue to pursue her research in sensitivity and anaphylaxis.

Morris successfully defended her dissertation, “The Relation Between Hypersensitiveness and Resistance,” in 1935 and was shortly thereafter elected to Sigma Xi.¹⁵ She presented a preview of her dissertation to the broader scientific community with an abstract at the 1935 annual meeting of the Society of American Bacteriologists titled “The Relationship of Antianaphylaxis to Antibody-Balance and to Immunity.”¹⁶ She followed that up with her first primary-authored manuscripts, “The Relation Between Antianaphylaxis and Antibody Balance (part I and part II)” the following year.¹⁷ In a footnote on the first page, she dedicated this paper to Bronfenbrenner, “who suggested these investigations, and to whom we are indebted for assistance, advice, and interest throughout the course of this study.”¹⁸

In the academic year following her doctorate, Morris was made a research fellow in bacteriology while maintaining her position in the Department of Ophthalmology. She was hired as a full-time instructor in bacteriology and immunology in the Department of Bacteriology and Immunology the following year.

The move to a new department provided new opportunities and new colleagues for Morris. In addition to Bronfenbrenner, who chaired the department, and Julianelle, Morris worked with assistant professor Philip L. Varney (AAI 1948) and the other instructors: Hiromu Tsuchiya and future Nobel laureate Alfred D. Hershey (AAI 1942), whom Bronfenbrenner had personally recruited. Her medical school teaching and laboratory responsibilities included bacteriology, and infection and immunity, which were required courses for second-year medical students.

Morris remained an instructor until 1942, when she was promoted to assistant professor of bacteriology and immunology. During that time, she interacted with new recruits to the department, including future AAI members Simon E. Sulkin (1945) and Carl G. Harford (AAI 1948). Her research shifted slightly toward the creation of more effective serums, potentially for viruses, work that was published in *The Journal of Immunology* (*The JI*).¹⁹

New Opportunities



Marion Morris, 1948
(colorized)

In the summer of 1943, Morris resigned from her position at Washington University. There is no record of why she left, but she quickly took a one-year appointment at Vassar College as an associate professor of plant biology.²⁰

After a year at Vassar, Morris returned to New York City and took a position at the Public Health Research Institute (PHRI) in the Division of Infectious

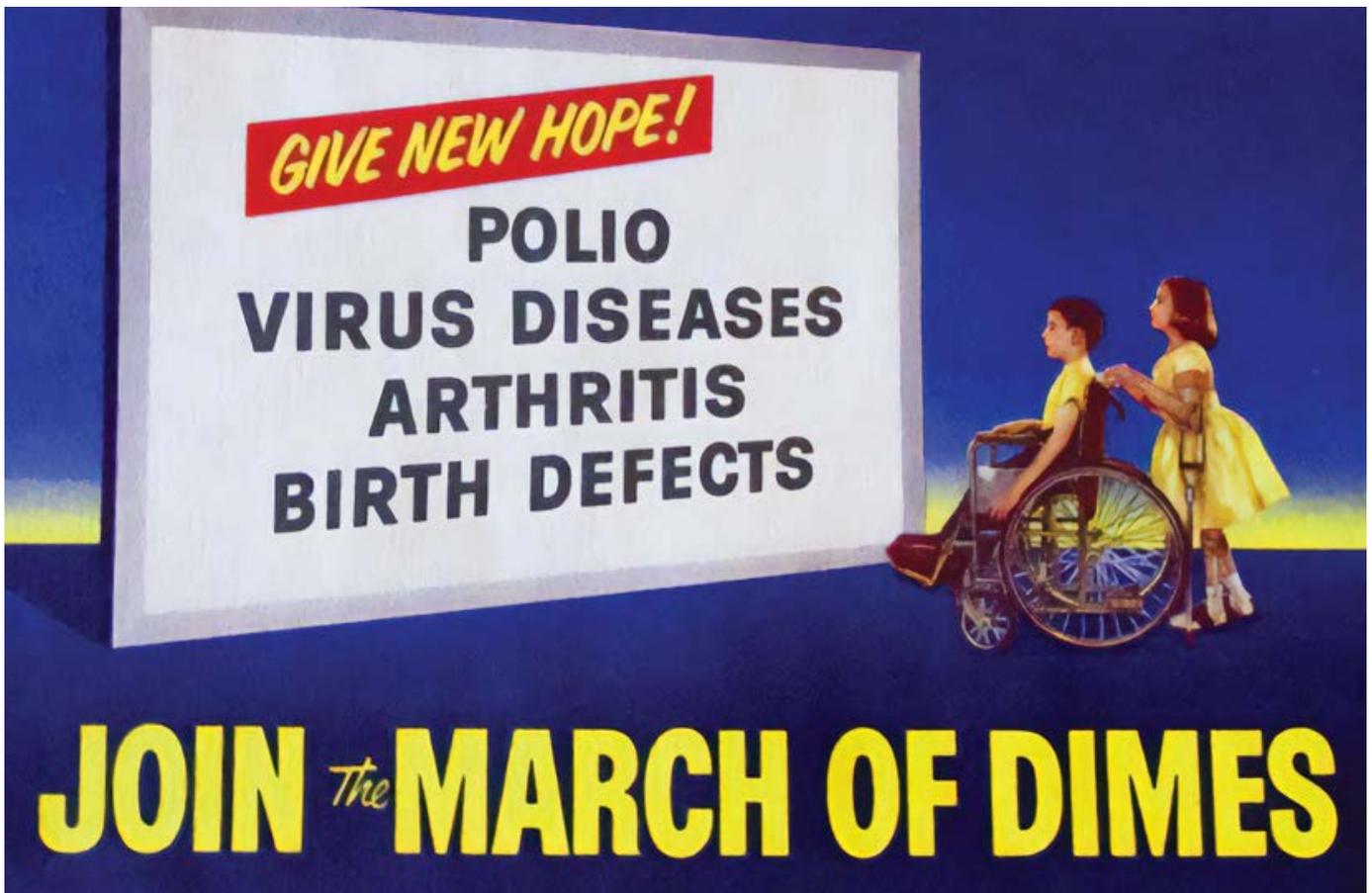
Diseases. Founded by Mayor Fiorello La Guardia in 1942 as an independent nonprofit research organization, PHRI initially had three divisions: Infectious Disease, Applied Immunology, and Nutrition and Physiology (later renamed Division of Biochemistry). The division of infectious diseases director was a familiar face for Morris. Louis Julianelle had been recruited from Washington University to become the division’s first director in 1942, which no doubt played a role in Morris coming to PHRI.²¹ As a pure researcher, Morris’s publishing output increased in her years at PHRI, all of which appeared in *The JI*. Morris later described this time as “all academic immunology—nothing you can make popular at all!”²²

National Foundation for Infantile Paralysis

In 1952, Morris left PHRI and bench science for the National Foundation for Infantile Paralysis (later renamed the March of Dimes), where she initially served as the assistant director of professional education in the Division of Scholarships and Fellowships. Morris played an uncelebrated but crucial role in numerous scientific investigations as she evaluated funding requests from all over the world.

One such instance occurred in March 1957, when she received a letter from Joseph Smadel (AAI 1937, president 1958–59), who had received his M.D. at Washington University School of Medicine the same year Morris had completed her master’s degree there. Smadel’s familiar tone suggests that the two had known each other for some time. He was writing on behalf of Carleton Gajdusek, whose NFIP funding had run out in January. Morris had recently asked Smadel about Gajdusek because she had not heard from him about his grant. Now Smadel had an answer for her: Gajdusek was “among the cannibals studying a most important new disease with neurological manifestations.”²³ The new disease was kuru, a prion-transmitted spongiform encephalopathy contracted by consuming human brain tissue. The Fore people of Papua New Guinea would consume the bodies of their deceased relatives and sometimes develop debilitating tremors and neurodegeneration.

Smadel acknowledged that “red tape” might prevent NFIP from extending the expired funding, as “with all the best intentions, we cannot put a man on a fellowship or on a staff appointment without having a warm body and a signature.” Morris agreed that funding through normal avenues was not “feasible” but evidently passed the request on to Thomas Rivers, the medical



March of Dimes poster, 1959

director at NFIP, who had the authority to make “certain funds” available in this highly unusual case—enough to get Gajdusek home and ease his transition from Australia’s Walter and Eliza Hall Institute to a new position at the National Institute of Neurological Disorders and Stroke (NINDS).²⁴

The success of the Salk and Sabin vaccines (approved in the United States in 1955 and 1961, respectively) led to a decline in contributions to the NFIP and thus necessitated difficult decisions about the future of the organization. In 1962, Morris’s division was eliminated as the organization pivoted towards birth defects and infant mortality. At the age of 60, Morris was without a job, which she recalled “was a blow. [It was] something that happened almost overnight and shouldn’t happen to anybody.” However, her varied skill set in the broader scientific field helped her find her next job.

Health Research Council



Marion Morris, c.1960

The Health Research Council (HRC) of New York City was the brainchild of Mary Lasker and the city’s commissioner of health, Leona Baumgartner, who first considered its creation in 1954. They approached Mayor Robert Wagner about creating a municipal research institute, the first of its kind, to fund public health research.²⁵ After a 1957 planning

session attended by 100 scientists from universities, government, and industry, a funding goal of \$1 per resident of New York City was established. Although the first year’s budget from the city was only \$1.1 million, by 1961, the budget was increased to \$8 million, meeting the initial goal.²⁶

By 1965, when Morris was the assistant scientific director, the HRC was funding the research of 172 individual scientists—most of whom were early career—on a wide range of public health and basic science investigations. Grant applications were open to all scientists on the faculties of colleges and universities in New York City or who were employed in municipal departments, and funded grants averaging \$14,000 per year.²⁷ The HRC also provided funding for institutional project grants for larger studies led by a primary investigator with a laboratory and staff.²⁸ The Council’s refurbishment program helped universities and hospitals reclaim disused spaces, creating more than 100 new laboratories in five years without any new construction.²⁹

Morris retired in 1971 and was a resident of New York City and an AAI member for the remainder of her life. She passed away on April 1, 1988.³⁰ Towards the end of her life, she was interviewed as part of a Smith College booklet highlighting notable alumnae. Looking back on her career, she stated, “I didn’t plan any of these things... Strength and energy fail as time moves on, but the psyche continues to produce great things.”³¹

Endnotes

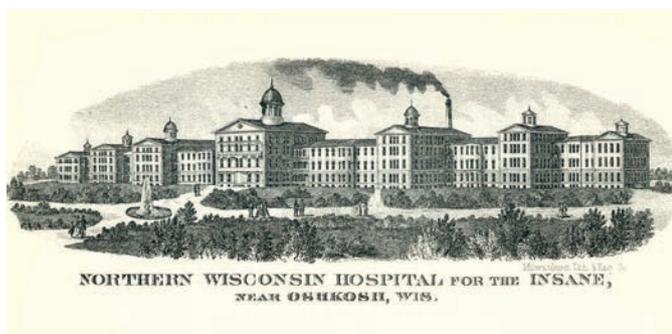
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Ludvig Hektoen: First Class in the Second City

Bird's-eye-view of the business district of Chicago, ca. 1898
Library of Congress

Before Ludvig Hektoen (AAI 1919, president 1926–1927) could begin what would become a long and illustrious career in Chicago, he needed to spend a year at the Northern State Hospital for the Insane in Oshkosh, Wisconsin.

As an aspiring medical student in 1884, Hektoen was unable to pay the tuition at the College of Physicians and Surgeons in Chicago, so he found work as an attendant at the asylum in his home state. The resourceful young man was swiftly put in charge of the hospital's pharmacy. There, he not only saved enough money to start medical school the next fall, but also shadowed the doctors and performed many autopsies himself, developing a lifelong interest in pathology and a head start to his professional education. He would go on to become a key figure at several of the institutes of research in Chicago and practically synonymous with the rise of medical science and immunology in the city.¹



Northern Hospital, 1885
Wikimedia Commons

Early Life

Hektoen's parents came to the United States from Norway by way of Canada in 1854. Nine years later, their first child, Ludvig, was born in Westby, Wisconsin, a community composed almost entirely of Norwegian immigrants. As a child, Hektoen spoke only Norwegian except at school. Even after beginning college at fourteen, half of his curriculum was in his native tongue. When he graduated with a B.A. in 1883, he had not yet taken a single course in science, but a friendship with a local physician in Westby inspired him to take a year of pre-med courses following graduation.²



Ludvig Hektoen, undated
University of Chicago
Library, Special Collections
Research Center

After finishing medical school as valedictorian in 1887, Hektoen had his internship at Cook County Hospital and, like many physician-scientists at the time, went to Europe for further study. Once back in Chicago, he quickly amassed a dizzying number of overlapping positions around Chicago: pathologist at the Cook County Hospital, physician at the Cook County Coroner's Office, and professor at not only the College of Physicians and Surgeons (now University of Illinois College of Medicine) but also Rush Medical College (RMC, now Rush University)—where he also served as curator of the medical history museum. By 1901, he had joint appointments as professor of pathology at RMC and head of the pathology department at the University of Chicago, both of which he held until retirement.³

HISTORY

At this time, the city of Chicago was growing rapidly thanks to industrialization and waves of immigration from Europe: the city more than tripled in population from 1880 to 1900.⁴ The 1893 World's Columbian Exposition showcased the city and promoted the idea that urban areas could be beautiful as well as functional. As the city grew, so did its capacity for medical research.

Hektoen's commitment to Chicago as a research center was tested in 1903, when Simon Flexner (AAI 1920) left the University of Pennsylvania for the Rockefeller Institute for Medical Research. Penn tempted Hektoen with Flexner's job as a professor of pathology. His peers, including William H. Welch, urged him to abandon Chicago and take the position at the more prestigious and well-established university. But Hektoen felt an obligation to the city that had given him so many opportunities and had such enormous potential at the turn of the century.⁵ He stayed and continued his contributions until he died in 1951.



Electrical Building, World's Columbian Exposition, 1893
Library of Congress

Rush Medical College

Rush Medical College was chartered in 1837, making it the oldest medical school in Chicago—exactly two days older than the city itself.⁶ Ten years later, the nascent institution distinguished itself as the first in the United States to confer a medical degree on an African American, David Jones Peck.⁷ By the turn of the 20th century, Rush had become the medical school of the University of Chicago, and “Rush doctors” were highly prized throughout the country, especially out west.

When Rush hired Hektoen in 1894, he was given a rather peculiar title as the result of professional rivalry. By this time, he was well known as a pathologist, but John Hamilton, the former Surgeon General of the United States, had already been named professor of pathology at RMC. Not a pathologist by training, Hamilton was given the position largely as a courtesy when he arrived in Chicago in 1893 as editor of the *Journal of the American Medical Association*. To justify the title, Hamilton wrote a textbook on pathology—a volume that Hektoen had reviewed scathingly. When Rush wished to hire Hektoen as chair of pathology, Hamilton remembered his critic and stridently objected, and the administration had to come up with the more creative “professor of morbid anatomy” title—at least until Hamilton's untimely death five years later.⁸



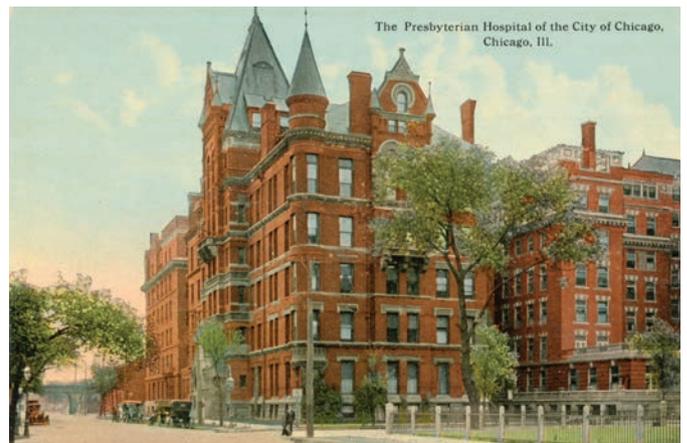
Rush Medical College, ca. 1913
Chicago History in Postcards

From 1898 to 1942, RMC served as the medical school of the University of Chicago, then became affiliated with the University of Illinois until 1969. Today it operates as the medical school of Rush University.

McCormick Memorial Institute

By the time he was 40 years old in 1903, Hektoen had authored one hundred publications, almost uniformly pathology case studies. But when he accepted a third concurrent position as the inaugural director of the John McCormick Memorial Institute, his career took a sharp turn toward more investigative research into immunity.

Edith Rockefeller and Harold McCormick both came from the families of wealthy industrialists. Edith's father was John D. Rockefeller, the oil magnate, and Harold was the son of Cyrus Hall McCormick, the inventor of the mechanical reaper



Presbyterian Hospital of the City of Chicago, ca. 1906
Wikimedia Commons



Harold Fowler McCormick & Edith Rockefeller, 1895
Wikimedia Commons

and head of International Harvester. When their first son was killed by scarlet fever in 1901, they decided to use a portion of their shared fortune to fund the John R. McCormick Memorial Institute for Infectious Diseases.

The institute's first location was in rented space at Chicago's Presbyterian Hospital (the teaching hospital of RMC), where Hektoen had been the pathologist since 1898.⁹ At the institute, he led the drive to provide free care to patients who suffered from many common diseases of the time. The institute treated over 14,000 low-income Chicagoans in its first two decades and had a 97% survival rate for scarlet fever patients. By 1916, it had produced and distributed over 100 million doses of the diphtheria vaccine.

In addition to its public health outreach, the McCormick Institute was the home of important research and development in both print and the laboratory. Under



Scarlet fever quarantine sign, ca. 1910
National Library of Medicine

Hektoen's editorship, the Institute founded *The Journal of Infectious Diseases* in 1904. Hektoen himself was increasingly interested in how the body produces antibodies and the mechanisms by which they work. He pioneered the use of the antibody curve as central to the study of antibody dynamics.¹⁰ During and immediately after the First World War, Hektoen explored how antibody production was affected by various agents that might be encountered on the battlefield, including mustard gas and different forms of radiation—research that ended up being vital in the ensuing atomic age and in the study of leukemia.¹¹

When the McCormick Institute was founded, George Dick was one of the first scientists to be recruited. In 1914, Gladys Dick joined her husband there, and ten years later the team identified a group A *Streptococcus* (*S. pyogenes*) as the causative agent of scarlet fever.¹² Using the erythrogenic toxin produced by the bacterium, they developed both a simple test for immunity and an immunizing vaccine for those the test showed to be susceptible.¹³ The couple was nominated for the Nobel Prize for their accomplishments in 1925, but no prize for Medicine was awarded that year.



George Dick, undated
University of Chicago Library, Special Collections Research Center



Gladys R. Dick, undated
Smithsonian Institution Archives

University of Chicago

The University of Chicago was just eight years old when it agreed to an affiliation with RMC in 1898. Founded in large part with a major donation from John D. Rockefeller, the university had sought to expand into medicine quickly, and the partnership with Rush proved beneficial to both institutions, providing the older RMC with necessary financial support, and giving the new university a ready-made medical school.

From 1901, when Hektoen started at the University of Chicago, through 1957, the Department of Pathology was chaired by an AAI president. As soon as he took the position, Hektoen hired H. Gideon Wells (AAI 1918, president 1923–24), who quickly established himself as a capable researcher and administrator. Wells put these skills to use at the end of WWI when he led two Red Cross commissions to Romania to battle typhus and famine, a trip that necessitated crossing portions of Russia in the middle of the Bolshevik Revolution.



H. Gideon Wells, ca. 1912
University of Chicago Library, Special Collections Research Center



Paul R. Cannon, undated
University of Chicago
Library, Special Collections
Research Center

Wells chaired the pathology department until 1940 and was succeeded by Paul R. Cannon (AAI 1929, president 1941–42). Cannon had wide-ranging research interests in his early career, but by the time of the Second World War, he was especially concerned with the immunological aspects of famine and starvation. Working with rat models, he showed that protein deficiency has a specific impact on immune response and developed standards for minimum daily protein intake.¹⁴

The Trial of Johann Hoch

In addition to his teaching and research work, Hektoen remained a practicing pathologist. In 1905, this expertise led to his involvement in one of the highest-profile murder cases Chicago had ever seen. Johann Hoch, a German immigrant, was facing trial for multiple cases of bigamy and the murder of his latest wife. Hoch had met Marie Welker through a newspaper ad and married her about a week later. Once she had sold her candy business and entrusted the money to Hoch, Welker took ill during the couple’s honeymoon and died within days.¹⁵



Johann Hoch, 1905
The Star Ledger

Hoch attributed his latest wife’s death to nephritis—just like his previous wife, he claimed. Welker’s sister suspected foul play, and when the body was exhumed, an autopsy revealed arsenic in her system. A police investigation quickly connected Hoch to dozens of similar cases of bigamy, fraud, and murder.

Hektoen examined the body and testified that he found no signs of nephritis. His testimony

contributed to Hoch’s conviction for the murder of his fifty-fifth wife. Further inquiry suggested that Hoch killed at least 15 women but perhaps as many as 50 after marrying them under various assumed identities.

As a pathologist, Hektoen regularly provided expert testimony in murder trials throughout his career, but none ever matched the spectacle and drama of the Hoch case. That same year, though, his successor at Chicago, H. Gideon Wells, participated in the identification of the remains of American Revolutionary War hero John Paul Jones by confirming a diagnosis of nephritis in the Admiral’s brandy-preserved corpse.¹⁶



Several of Hoch’s alleged wives, 1905
The Star Ledger

Parrot Fever

While on a 1930 trip to the Hygienic Laboratory in Washington DC, Hektoen found himself on the wrong side of research into psittacosis, or parrot fever. Since 1924, he had been serving in various leadership and consulting roles with the National Research Council and the United States Public Health Service, which often took him to the nation’s capital.¹⁷ During this year-long visit, he contracted psittacosis even though he had not come within 30 feet of any lab working on the disease. As he was the eleventh person at the Hygienic Laboratory to be infected in a brief period, US Surgeon General Hugh Cumming stepped in and temporarily halted research.

The rapid spread of psittacosis among physicians and lab staff turned out to be a happy accident that led to a new understanding of how it could be spread. The disease was unknown in the United States until a pandemic in 1929–1930, caused by the importation of large numbers of parrots for Christmas.¹⁸ It was initially believed to be transmitted primarily from close contact with the birds. Still, the local epidemic in the Hygienic Laboratory was evidence that the



A sailor brings home a pet parrot from his travels on this *Saturday Evening Post* cover, 1929

bacteria could be carried in airborne dust particles of bird droppings. Spurred by the high profile of Hektoen's illness, Cumming reorganized psittacosis research at the laboratory, staffing the labs only with workers who had developed immunity to the disease from prior infection. Hektoen and all but one of the other affected scientists recovered with the help of convalescent serum.¹⁹

Lasting Contributions



Ludvig Hektoen, undated
University of Chicago
Library, Special Collections
Research Center

One of Hektoen's most enduring contributions to immunology came when he was 70. With William H. Welker, he developed a method of adsorbing antigen to aluminum hydroxide; following intramuscular injection, the antigen would continue to stimulate antibody production for months.²⁰ Aluminum hydroxide is still one of the most used vaccine adjuvants.

Hektoen remained active in all of these capacities around Chicago and with national organizations well into his seventies. He lived to see

the McCormick Memorial Institute renamed the Hektoen Institute in his honor in 1943. His accomplishments are far too many to list here; for more about his work and other immunology stories in Chicago, visit the History exhibit at **IMMUNOLOGY2024™**.

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Material Culture of Immunology: “Jeryl Lynn Mumps Virus Cannister”

This series highlights objects in museums connected to the history of immunology. Material culture consists of the physical objects that help us understand cultural and social relations. These artifacts illustrate the role of immunology throughout history.

This unassuming stainless-steel canister played a crucial role in saving millions upon millions of children from the effects of mumps. It was one of five vessels that held the seed stock



Seed stock cannister for Jeryl Lynn Strain
National Museum of American History

for the Jeryl Lynn strain of mumps virus used to produce over three billion doses of vaccine.

The Jeryl Lynn strain was named after the daughter of Maurice Hilleman¹ (AAI 1949), a microbiologist and immunologist who had previously developed a vaccine for Japanese B encephalitis during the Second World War. Hilleman also discovered antigenic shift and drift in influenza and developed a vaccine that help prevent a serious flu pandemic in 1957.

Five-year-old Jeryl Lynn woke her father up at 1:00 a.m. on March 23, 1963, complaining of swelling and pain in her throat. Hilleman quickly diagnosed mumps, then drove to his laboratory at Merck to retrieve cotton swabs and nutrient broth. He took these supplies home, swabbed Jeryl Lynn's throat, and returned the sample to his lab.²

Hilleman attenuated the mumps virus by repeatedly passing it through chicken embryo cells. In 1966, one of the first children to receive a dose of the experimental vaccine was Jeryl Lynn's own sister, Kirsten.

Later, the seed stock for the Jeryl Lynn strain was placed in five 15-liter cannisters for safe storage. By 2015, however, the green neoprene stoppers had started to fail. Merck scientists

had to carefully transfer the seed stock to new containers without contaminating it. Failure could have resulted in a global shortage of mumps vaccine while new seed stock was produced, a process that would have taken up to seven years.³

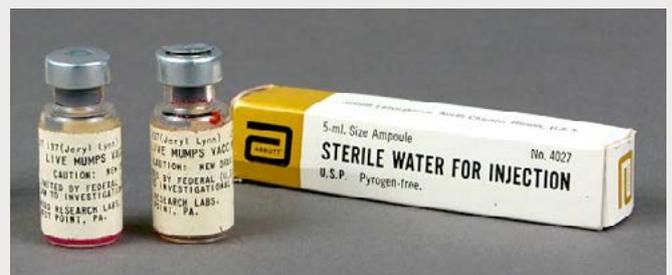
The transfer was successful, the vaccine supply was uninterrupted, and in 2017, the Hilleman family donated this cannister along with other artifacts from Hilleman's life, including his lab coat and several of his many vaccines, to the Smithsonian.

Over his long career, Hilleman was responsible for developing over 40 vaccines, including eight of the current standard childhood vaccinations. His vaccines continue to save millions of lives every year.⁴

Maurice Hilleman's cannister, lab coat, and vaccines are held in the Division of Medicine and Science at the Smithsonian National Museum of American History.

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Vials of investigational live mumps vaccine (Jeryl Lynn Strain)
National Museum of American History

HISTORY

Material Culture of Immunology: “First Flight”

This is the first in a new series of features highlighting objects in museums connected to the history of immunology. Material culture consists of the physical objects that help us understand cultural and social relations. These artifacts illustrate the role of immunology throughout history.

The halter and lead pictured at right were worn by First Flight, a horse that was the world's sole source of botulinum antitoxin for more than 10 years.

First Flight was always a difficult horse to lead. Although he was bred as a racehorse, he wasn't cut out for the track. For a time, he found work in the Caisson Platoon at Arlington National Cemetery, but even the quieter crowds there made him nervous. In 1978, First Flight got a transfer to the U.S. Army Medical Research Institute of Infectious Disease (USAMRIID) at Fort Detrick in Frederick, MD, to be a living factory for antitoxin against the most toxic substance in the world.



First Flight's Harness and Lead
National Museum of American History



Botulism antitoxin serum, 1990
National Museum of American History

To produce the first botulinum antitoxin, First Flight was injected with modified toxoids from all seven strains of *Clostridium botulinum*, then with the live bacteria once he developed immunity. From his blood was produced the heptavalent botulinum antitoxin (HBAT) that the Pentagon would eventually issue to troops deployed to Iraq in the Gulf War, reflecting the concern that Iraqi President Saddam Hussein would use biological weapons. First Flight's HBAT has also been used to treat infant botulism and foodborne botulism in adults.

First Flight was known as a spirited horse who would nip at inexperienced technicians, but a quick tug on his lead would remind him of his duty. He would then stand patiently for the blood draw before prancing off to the stable to boss around the other horses. The halter and lead bearing his name helped make this important antitoxin possible.

First Flight's halter and lead are held in the Division of Medicine and Science at the Smithsonian National Museum of American History.