



**Robert Austrian**

1916–2007

BIOGRAPHICAL

*Memiors*

*A Biographical Memoir by  
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and John B. Robbins*

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NATIONAL ACADEMY OF SCIENCES

# ROBERT AUSTRIAN

April 12, 1916–March 25, 2007

Elected to the NAS, 1979

Robert Austrian, M.D., known to colleagues and friends as Bob, was a modest gentleman with nothing to be modest about. Austrian's professional career as a clinician and scientist spanning more than 60 years was devoted to the conquest of disease caused by the leading bacterial pathogen, *Streptococcus pneumoniae* (the pneumococcus). It was largely through his efforts that pneumococcal disease was recognized as a continuing problem despite the introduction of antibiotics, which triggered the development of the first licensed pneumococcal vaccine. Born in Baltimore in 1916 to Florence Hochschild and Charles Austrian, a prominent internist and expert in pulmonary diseases, Robert Austrian grew up in a house along Baltimore's Doctors' Row. His decision to enter medicine was influenced by the respect he held for his father, who was described by Bob as a keen observer with extraordinarily good judgment and a hard act to follow.



A handwritten signature of Robert Austrian in dark ink, written in a cursive style.

By Jeffrey N. Weiser  
and John B. Robbins

While a medical student at Johns Hopkins (1937–41), Austrian began his studies on pneumococcus with Dr. Barry Wood, a leader in the field of pneumococcal pathogenesis, embarking on a path that Austrian would follow throughout his career. Because of the introduction of antimicrobial chemotherapy beginning with the sulfa drugs in the 1930s, it was an exciting period in medicine and, in particular, infectious diseases, Austrian's chosen field. After serving on the Typhus Commission of the U.S. Army in Burma during World War II, Austrian returned to his interests in pneumonia and the pneumococcus through training at New York University in the microbiology lab of Dr. Colin MacLeod. Dr. MacLeod had previously conducted groundbreaking experiments with Oswald Avery using DNA to transform pneumococci and establish the role of DNA as the genetic material. Austrian described the year he spent in Dr. McLeod's laboratory as the most intellectually exciting of his life. The following year, while still at

Bellevue Hospital in New York, he joined the cardiopulmonary laboratory of Dr. André Cournand, a pulmonary physiologist and later a Nobel laureate. He returned to Baltimore to be Chief Medical Resident and then joined the faculty at Johns Hopkins University. Three years later, Dr. Perrin Long, a former associate from Hopkins and the first person to introduce sulfa chemotherapy to the United States, recruited Bob to Kings County Hospital in Brooklyn. Bob convinced Dr. Long to allow him to set up his own diagnostic microbiology laboratory, distinct from that of the hospital's, where he instructed house staff on the importance of obtaining sputum and blood cultures prior to initiating antibiotics. By this time, penicillin was in widespread use against pneumococcal pneumonia, and as Austrian recalled, "the drop in mortality was so dramatic that most people began to feel this illness was no longer a common or serious one and that they no longer felt it was necessary to identify pneumococci." As a result of his meticulous analysis of clinical specimens, the sensitivity of diagnosis was considerably enhanced. Additionally, his skilled application of the quelling reaction using specific sera allowed him to distinguish prevalent serotypes, even though this involved a laborious procedure, based on a technique first described in 1902 by one of his scientific heroes, Franz Neufeld, that was becoming a lost art after serum therapy was no longer in use. It was in this setting at the Kings County Hospital, a facility of over 3,500 beds and one of the largest acute care centers in the country, that Austrian made his first seminal observations on the epidemiology of the pneumococcus, despite the warnings from his colleagues that he would find few cases of pneumococcal pneumonia.

Austrian was an astute clinician. Among his early insights in medicine was a report in 1957 showing that the association of meningitis, pneumonia, and endocarditis first described in 1881 by Sir William Osler, another heroic figure to Bob—is caused by invasive pneumococcal infection, a syndrome now referred to as Austrian's Triad. Throughout his career as a clinician-scientist, he learned from his patients, and his experience at the bedside both dictated the direction of his research and shaped his approach to problem solving. Austrian liked to relate the following story from the early days of antibiotic therapy. In 1949, he treated a young woman at Hopkins who was severely ill with lobar pneumonia with chlortetracycline, the same year the antibiotic was introduced. His concerns for the appropriateness of her medication were relieved the following day by her rapid recovery. Although initially very pleased with himself for her prompt response to his therapy, he later learned that each antibiotic capsule was found unconsumed under her pillow after the woman's discharge from the hospital. In describing these events, Austrian remarked, "The experience taught me, first-hand,

a lesson in therapeutics I have never forgotten and brought home clearly the portent of my father's comment that most patients get well in spite of doctors." Clearly, this was one of the experiences that contributed to his deep skepticism of the prevailing wisdom of the day: that antibiotics were required for a positive outcome, and if used reliably, would eliminate fatalities from pneumococcal pneumonia. Austrian was well prepared to understand and appreciate the limitations of the new era. In 1896, Osler, considered by many the father of modern medicine, established a tradition at Johns Hopkins Hospital of annually reviewing all cases of pneumonia. In Austrian's book, *Life with the Pneumococcus*, he related that "The tradition endured, and I came under its influence at the time of the introduction of sulfonamides." Through the careful use of laboratory-based diagnosis and serotyping, his study of pneumococcal pneumonia treated by the medical service at Kings County Hospital between 1952 and 1962 demonstrated a persistently high rate of mortality (17%) in the antibiotic era, particularly in cases of bacteremic disease where, in fact, penicillin therapy had little or no effect on the outcome of infection among those destined to die within the first five days. This sobering finding to health care providers, who had incorrectly assumed that pneumococcal disease was no longer a significant public health concern after the discovery of penicillin in the 1940s, was published in 1964 in a landmark study performed in collaboration with Jerome Gold. They concluded that highly effective antimicrobial drugs must be supplemented by other measures, and that prophylaxis would be the only means of reducing the still significant mortality rate—a goal that occupied the rest of his career.



Austrian, always a keen student of medical history, was able to appreciate and incorporate the lessons of his predecessors in his own work. In fact, the initial development of a pneumococcal vaccine dated back to 1911, when Sir Almroth Wright attempted to prevent the devastating effects of pneumococcal disease among the new recruits to the

South African gold mines. Interestingly, Austrian's father had been introduced to Sir Almroth by Osler in 1912 during a visit to England. Wright's efforts at preventing disease by mass vaccination of miners were unsuccessful because the complexity and extent of antigenic variation among isolates had not yet been fully appreciated. Much later, by using purified capsular polysaccharides from the four most prevalent pneumococcal serotypes ('types'), MacLeod, Bob's former mentor at New York University, together with Michael Heidelberger, produced and tested in American soldiers the first successful vaccine, which was eventually licensed in 1947 as a heptavalent preparation. However, with interest in pneumococcal infection then being at its nadir, MacLeod's vaccine was not used enough to make it commercially feasible and by the 1950s it was withdrawn from the market. Having convincingly established the continued public health burden of pneumococcal infection by the early 1970s, Austrian, now the John Herr Musser Professor and Chairman of the Department of Research Medicine at the University of Pennsylvania (1962–86), was able to resurrect MacLeod's approach to developing the vaccine. By this time, many more pneumococcal 'types' had been delineated, and largely through his extraordinary work bridging laboratory and bedside, the relative prevalence of these types was determined. Of the 83 antigenically distinct 'types' known at the time, he was able to show that the inclusion of capsular polysaccharide of 14 'types' would in aggregate be sufficient to provide protection against the vast majority of currently circulating pneumococci. Austrian followed these epidemiological studies under the aegis of the National Institutes of Health by returning to the gold miners of South Africa to conduct a large, randomized clinical trial to test his vaccine. In 1976, he reported that the new vaccine was both safe and effective at preventing pneumococcal disease. Despite this achievement, it remained uncertain whether the vaccine would ever reach the public, since its manufacturer decided around this time to leave the vaccine business. Austrian was able to resurrect the vaccine again by convincing Maurice Hilleman, a virologist in charge of vaccines at Merck, to take on inherent difficulties of large-scale production of this multi-component product. His scientific efforts culminated in 1977 with licensure of a polyvalent pneumococcal vaccine containing purified capsular polysaccharide of 14 'types.' In 1983, the vaccine was expanded to contain 23 'types' that accounted for 85 percent of bloodstream infections associated with pneumococcal pneumonia. Austrian's vaccine was recommended for routine use in all persons at age 65, and those younger with increased risk. This vaccine, which has now been administered to millions, remains the most complex vaccine ever produced.

Throughout his professional career spanning more than six decades, Austrian was remarkably focused on one problem: the pneumococcus. His single-minded assault on

Austrian's career spanned the use of serum therapy, chemotherapy, antibiotics, and several generations of vaccines, each of which was initially believed to offer a final solution to the problem. The pneumococcus, however, has proven to be a particularly elusive and adaptable foe.

this pathogen was best summarized by the words of Lewis Thomas, M.D. in the forward to *Life with the Pneumococcus*:

*The major figures in American biomedical research come in several quite different classes. There are those who shift swiftly from problem to problem, sometimes leaping freely from one biological discipline to another and then back again, lighting finally on a soluble problem as though by accident. There are others who meditate on a single puzzle for years at a time, scarcely moving, and then, obsessed overnight by the idea of a lifetime, swoop down like night owls on the single answer.*

*And there are those who pick out the one problem that will preoccupy them for an entire career of hard work and then just keep at it, year after year. This may seem the safest way to live a life in science, but it is actually, in real life, the chanciest of all gambles, like putting all your chips on a single number, play after play, until all your money runs out.*

*Robert Austrian's career has been this last kind. He became fascinated by a single microorganism, *Streptococcus pneumoniae*, long ago, and simply stuck with it. As the years went by, some of his colleagues came to believe that he was simply stuck with it. Finally, not as a result of good luck or any nocturnal revelation or unforeseen laboratory accident, but as the uncommon reward for steady, meticulous, logical experimentation, he got what he was after: a polyvalent vaccine against pneumococcal infection.*

*The papers in this book are a nice historical record of how science goes when it is going slowly but going well. They are also a lesson in what most savvy investigators take on faith: that if you can learn enough new things about living things at a fundamental level, sooner or later you may have the chance, as Austrian has had, to turn basic science into applied science and, at last, into a useful product.*

Remarkably, after this passage was written and the book appeared in 1985, Dr. Austrian spent another 22 years, until the day prior to his death in 2007, at his microscope using the quelling reaction to monitor the evolution of pneumococcal ‘types.’ As an Emeritus Professor at the University of Pennsylvania from 1986, he single-handedly typed more than 10,000 clinical isolates sent to him from across the globe, serving as a World Health Organization reference laboratory.

Austrian’s career spanned the use of serum therapy, chemotherapy, antibiotics, and several generations of vaccines, each of which was initially believed to offer a final solution to the problem. The pneumococcus, however, has proven to be a particularly elusive and adaptable foe. Bob would have been the first to warn us not to underestimate it or to be overly confident that the quest is complete. In fact, the use of the polyvalent polysaccharide vaccine has remained controversial. Efficacy studies leading to licensure were carried out in healthy young adults in Africa, but the vaccine was used primarily in immunocompromised and elderly populations in developed countries. To address these concerns, in 1991, he and his colleagues reported a large, carefully performed post-licensure study in the *New England Journal of Medicine*, demonstrating that polyvalent pneumococcal vaccine was efficacious in preventing invasive pneumococcal infections in immunocompetent patients in the U.S. with indications for its administration. Despite confirmation of protection against the most serious form of the disease, bacteremic pneumococcal pneumonia, skepticism about the vaccine’s effectiveness against nonbacteremic pneumonia continued because of limitations in the microbiological diagnosis of pneumonia, waning immune responses in the increasingly elderly population that received it, and the inherent complexity of a vaccine with 23 components. Until just prior to his death in 2007, Bob continued to engage and refute the naysayers by pointing out these issues.

Austrian’s landmark vaccine helped to establish that multi-component polysaccharide vaccines are feasible. In 2000, the first pneumococcal vaccine in which the polysaccharide was linked to an immunogenic protein was introduced, and this extended the usefulness of polysaccharide-based vaccines to children. Pneumococcal conjugate vaccines given to children have been highly effective in reducing the burden of childhood disease as well as transmission, resulting in protection of unvaccinated populations. This herd immunity that results from reduced transmission from children has led to decreased acquisition of the organism and a remarkable reduction in the overall incidence of pneumonia in adults—the ultimate goal of Austrian’s career. The decreasing incidence of the disease following widespread vaccination has also proven that Austrian was absolutely correct

about the relative importance of the pneumococcus in the etiology of pneumonia. Austrian's vaccine and those that followed stand out as our greatest victory against the foe William Osler

labeled "the captain of the men of death." The emergence and dissemination of pneumococcal resistance to penicillin beginning in the 1960s, and eventually to many other commonly used antibiotics, has highlighted the importance of anti-pneumococcal vaccination to the practice of medicine. Fortunately, these vaccines were available when most needed to help turn the tide against the rising problem of antibiotic resistance. Dr. Harvey Friedman, Austrian's long-time infectious disease colleague at the University of Pennsylvania, said in his nomination of Bob for the Maxwell Finland Award for Scientific Achievement from the National Foundation of Infectious Diseases (2001), that "Dr. Austrian's foresight and perseverance were truly remarkable. What Dr. Austrian did to solve a major human disease problem, almost totally by himself, is virtually unique in modern day medicine."

Robert Austrian was widely recognized for his accomplishments and was the recipient of numerous awards and honors, including the Philadelphia Award (1979); the Bristol Award from the Infectious Diseases Society of America (1986); election to membership in the American Philosophical Society (1987); election to senior membership, Institute of Medicine, National Academy of Sciences (1992); and the Sabin Gold Medal in 2002. He was awarded the prestigious Albert Lasker Clinical Medical Research Award in 1978 for "his perseverance in the development and clear demonstration of the efficacy of a purified vaccine" for pneumococcal infection. He was elected to the National Academy of Sciences in 1979.

Always elegant, Bob was never seen without a suit and tie. He was the consummate wise physician, a remarkable scholar, epidemiologist, microbiologist, and valued colleague. He changed the practice of medicine, and in the process left the world a healthier place.



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