

2004 Albert B. Sabin Gold Medal

Address Delivered by Award Recipient

William S. Jordan, Jr., M.D.

With a Tribute by John R. LaMontagne, Ph.D.

May 25, 2004
Arlington, Virginia

INTRODUCTION

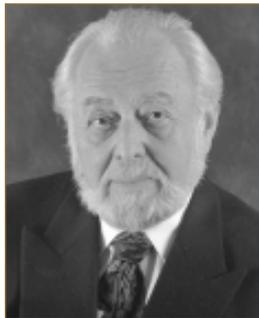
by *H.R. Shepherd, D.Sc.*
Chairman, The Albert B. Sabin Vaccine Institute

The Sabin Vaccine Institute pursues Dr. Albert B. Sabin's vision of a world protected from disease by vaccines. The annual awarding of the Sabin Gold Medal has always been among our most meaningful traditions. The 2004 award was presented in May to an icon in vaccine research, William S. Jordan, Jr., M.D., at a ceremony in Arlington, Virginia, during the 7th Annual Conference on Vaccine Research, co-organized by the Sabin Vaccine Institute.

The positive impact of vaccines on the health and well being of humanity continues to be a marvel of our modern world. Vaccine improvements, new vaccines, and vaccines in the pipeline represent an advancing field of science that brings untold preventive benefit to millions around the world. Along with his career in vaccine research, Dr. Jordan has engaged in compiling the record of scientific advancements in the field. His name is synonymous with both vaccine research and the compendium—*The Jordan Report*—that for 25 years has been a repository for advances in the vaccine field.

The Sabin Gold Medal Advisory Committee, chaired by Maj. Gen. Philip K. Russell, M.D. (USA Ret.), selected Dr. Jordan for this honor after canvassing 300 members of the scientific community. We are pleased to recognize Dr. Jordan with this honor, noting his exemplary contributions in the vaccine field and commitment to lifesaving medical discoveries.

Dr. Jordan's rigor in medical research is clear from his detailed and comprehensive account of the vaccine field. His stamina and determination are evident in the style and command of his lecture, delivered to several hundred fortunate enough to have been in attendance. In addition to his remarks on the "Wonderland of Vaccines," guests were regaled by a rousing tribute to him from a protégé, John R. LaMontagne, Ph.D., deputy director, National Institute of Allergy and Infectious Diseases. Both speeches are printed in this booklet.



H.R. Shepherd, D.Sc.

With the Sabin Gold Medal Advisory Committee, and on behalf of the Board of Trustees of the Institute, I congratulate Dr. Jordan. I invite you to take a recollective journey of a wonderland of vaccines with him. He is a most capable eyewitness and guide. His address is recommended reading for all in the vaccine field.

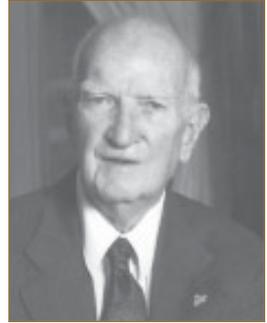
WILLIAM S. JORDAN, JR., M.D.
2004 ALBERT B. SABIN GOLD MEDAL RECIPIENT

William S. Jordan, Jr., M.D., physician, teacher, and noted vaccine researcher, began his distinguished career in the field of preventive medicine more than 60 years ago. During the course of his career he advanced national and global disease prevention strategies as well as promotion of vaccine development research.

He helped launch a unique program at the National Institute of Allergy and Infectious Diseases that today serves to accelerate vaccine development and focus needed attention and resources on new vaccines and vaccine improvements. Dr. Jordan established an annual scientific review, known as *The Jordan Report*, considered by many in the scientific community to be the most complete reference on vaccine research and development available.

A graduate of Harvard Medical School, Dr. Jordan held faculty posts at the Western Reserve University in the Department of Preventive Medicine, at the University of Virginia School of Medicine as chair of Preventive Medicine, and subsequently at the University of Kentucky as dean of the College of Medicine. He also served as director of the Commission of Acute Respiratory Diseases of the Armed Forces Epidemiological Board. He spent a sabbatical year at the London School of Hygiene and Tropical Medicine, University of London.

From 1976 to 1987, Dr. Jordan served as director of the Microbiology and Infectious Diseases Program at the National Institute of Allergy and Infectious Diseases, National Institutes of Health. A key part of his efforts there, where he remains active today on a voluntary basis, involves the advancement of vaccine research initiatives. He is author or co-author of more than one hundred papers, textbook chapters and two books.



William S. Jordan, Jr., M.D.



The Albert B. Sabin Vaccine Institute gratefully acknowledges unrestricted grants from Aventis Pasteur, Wyeth, Merck & Co., and other support used to underwrite the 2004 Albert B. Sabin Gold Medal ceremony and this publication.

TRIBUTE TO
WILLIAM S. JORDAN, JR., M.D.

*by John R. LaMontagne, Ph.D.
Deputy Director,
National Institute of Allergy and Infectious Diseases*

I cannot tell you how pleased and honored I am to introduce this year's recipient of the *Albert B. Sabin Gold Medal Award*—Bill Jordan. You see I have had the great privilege of working for Bill and seeing first hand his ability to make a difference. Actually, Bill and I started our careers at NIH about the same time. We came into the NIAID in 1976 in the maelstrom that was the National Influenza Immunization Program or NIIP, but more easily recognized as the “Swine Flu” program. I was the newly hired Influenza Program officer; he was the director of the Microbiology and Infectious Diseases Program. His tremendous experience in dealing with respiratory infections and influenza in particular was invaluable to me. His knowledge of the field was exceptional and his experience unparalleled—I learned a lot!

I cannot think of anyone more deserving of the recognition of this award than Bill—he grew up with the issues that are at the core of the *Albert B. Sabin Gold Medal Award*. He shares Albert Sabin's commitment to excellence in research and to making a difference in the health of people.

He was born in Fayetteville, North Carolina, and received his undergraduate degree at the University of North Carolina. He began his medical education at Harvard Medical School in 1938 and received his M.D. degree cum laude in 1942, just six months after World War II started. It was also in Boston that he met his wife Marion. He then entered military service as a physician in the Navy and was first stationed in Reykjavik, Iceland. After D-Day he returned to the United States and served for a short time at the Navy Hospital in Bethesda before being assigned to sea duty in the Pacific Theater until the end of the war.

In 1946 he returned to Boston as an assistant resident at the fabled Boston City Hospital, where he rejoined Dr. Maxwell Finland and Dr. John Dingle. He then moved to Cleveland in 1947 to rejoin Dr. Dingle as a member of the Department of Preventive Medicine with a joint appointment in the Department of Medicine. Bill's move

to Cleveland was critically important because it reunited him with his colleague, Dingle, and where he also directed his considerable energy and talents towards a career in epidemiology. It was in Cleveland that he participated the “Cleveland Family Study”—a longitudinal study of families living in Cleveland.

This study is a classic in epidemiology and resulted in a series of 16 papers that catalogued the health experiences of these families in detail. The study revealed the key importance of respiratory and enteric infections in the health of everyday families. Bill and his collaborators immortalized this study in their landmark book, *Illness in the Home*, a true classic of infectious diseases. This study illustrates clearly the rigor and care Bill used in his collection of data and in their analysis. The study not only documented the impact of these infections on family health, but it also established that many of the etiologic agents responsible for these illnesses were unknown.

In 1958, Bill joined the faculty of the University of Virginia School of Medicine, where he continued his work on respiratory disease. He also assumed greater national prominence in medical affairs by his leadership as director of the Commission of Acute Respiratory Diseases, a component of the Armed Forces Epidemiological Board for six years. In 1967, he left Virginia to become the Dean of the College of Medicine at the University of Kentucky in Lexington. And as I mentioned earlier, he joined the NIH in 1976 as the director of the Microbiology and Infectious Diseases Program in the National Institute of Allergy and Infectious Diseases, the point where our association began.

His tenure at the NIAID was one of great progress. He was the creator and chief advocate for a new effort, which he dubbed the “Accelerated Development of Vaccines.” He sensed that scientific progress was accelerating and that the very pace of discovery was going to yield many new ideas for vaccines of all kinds. It was this marriage of new science and the practical application of that science in the form of new vaccines and other interventions that motivated him and us—his subordinates in the Microbiology and Infectious Diseases Program. The idea will not be a surprise to anyone who knows Bill. He quickly grasped the possibilities and translated that enthusiasm to us—we knew he was onto something and we also felt he was right. New vaccines to prevent a whole series of infectious diseases were possible—all we needed to do was to apply ourselves to this task and to marshal the resources we need to do this work. It was an important moment for me and to others in the institute. His leadership and skill in

communicating this message to us was so important. It was a powerful tonic! His energy and enthusiasm for this work was infectious.

He was eager to track progress and asked for an annual report on our efforts. Those of us who worked on the report called it “*The Jordan Report*.” For many years this report was an internal document. It became an important annual task for staff in the institute, and in 1993 we decided to make the report more widely available but continued to call it “*The Jordan Report*.” This made sense to us, Bill had name recognition—we didn’t! It is now recognized as the authoritative report of progress in vaccine development, and its audience is international. This is a fitting tribute to Bill; it reflects his commitment to research and to preventive medicine.

The NIAID’s programs in vaccine research and development were very productive during his tenure as director of the research program. Hepatitis B vaccines became a reality, so did vaccines to prevent *Haemophilus influenzae* type B and pneumococcal polysaccharide vaccines. Efforts in the development of improved influenza vaccines were also key successes. The large clinical trials of inactivated vaccines performed in 1976 and 1978 led to greatly improved inactivated vaccines

Dr. John R. LaMontagne received his Ph.D. from Tulane University in 1971. In 1976, he came to the National Institutes of Health (NIH) as the Influenza Program officer at the National Institute of Allergy and Infectious Diseases (NIAID). He became the program officer for the Viral Vaccines Program in 1983, and the Influenza and Viral Respiratory Diseases program officer in 1984. Beginning in 1986, Dr. LaMontagne assumed the role of director of the AIDS Program. In 1987 he was appointed director of the Microbiology and Infectious Diseases Program, which became a division in 1988. Dr. LaMontagne was appointed deputy director of the NIAID in February 1998.



Dr. LaMontagne has made significant contributions to the national and international effort against emerging and re-emerging infectious diseases, including biodefense activities, and is recognized internationally for his leadership in this area. He played a central role in the organization of the Multilateral Initiative on Malaria, an international effort involving research, control, and development agencies from the United States, Europe, and Africa. In addition,

and major strides were made towards the development of an attenuated, live virus influenza vaccine.

Bill's contributions to the field were not restricted to vaccines. Under his direction we were able to confirm the value of antiviral drugs for herpes and for influenza. He was also a forceful advocate for research on the neglected diseases—malaria, schistosomiasis, filariasis, and other parasitic diseases. This led to the creation of the International Collaborations in Infectious Disease Research (ICIDRs). This was a very creative initiative that stimulated research collaborations and partnerships between research institutions in the United States and research groups in the developing world.

So it is no surprise that Bill is this year's recipient of the *Albert B. Sabin Gold Medal Award*. Bill embodies all of the elements that make a Sabin Award winner—his commitment and belief that research is the key to new developments in vaccinology is unquestioned; his commitment to a rigorous scientific approach in the pursuit of vaccines is unassailable; and his commitment to the translation of basic research into tangible interventions that benefit people is unambiguous. It is my great pleasure and honor to introduce Bill Jordan, the Albert B. Sabin Gold Medal Award recipient for 2004.

he serves as a member of the Scientific Advisory Groups of Experts on Vaccines and Biologicals as well as for Vaccines and Immunization for the World Health Organization (WHO). He chaired the WHO Task Force on Strategic Planning for the Children's Vaccine Initiative, advises the Pan American Health Organization on their programs in vaccine research implementation, and serves as a member of the board of the Global Alliance for Tuberculosis Drug Development. His administrative leadership at NIH includes membership on the NIH Community Advisory Board for Security and the recently formed NIH Ethics Advisory Committee.

Dr. LaMontagne is the recipient of many awards for his scientific accomplishments, including the PHS Special Recognition Award for leadership in childhood vaccine research programs, the Surgeon General's Certificate of Appreciation, the Presidential Meritorious Executive Rank Award, the Distinguished Executive Award for his work in the areas of infectious disease research of global health relevance, the Secretary's Award for Distinguished Service for leadership of acellular pertussis vaccine trials, and most recently the Secretary's Award for Distinguished Service for design and implementation of critically important biodefense strategies.

REMARKS UPON ACCEPTANCE OF THE 2004 ALBERT B. SABIN GOLD MEDAL

by WILLIAM S. JORDAN, JR., M.D.

I propose to take you and our knowledgeable audience through my personal looking glass to my Adventures in Vaccine Land, a world populated by many talented vaccinologists, an appellation attributed to Jonas Salk. I hope you will agree that Vaccine Land is truly a Wonderland. One of its great vaccinologists was Dr. Sabin. It was my privilege to know him well, as you will learn.

But let's begin with influenza, the initial problem Dr. LaMontagne and I had to deal with when we began our careers together in NIAID at NIH.

Influenza

I had arrived as director of the Microbiology and Infectious Diseases Program (now the Division of Microbiology and Infectious Diseases), and Dr. George Galasso had just recruited Dr. LaMontagne to join him in his branch. Dr. LaMontagne became the Influenza Program officer, just in time for the 1976 Flu episode, called by some a fiasco. An unusual influenza A virus appeared at Fort Dix. A single fatal case in a private provoked consternation throughout the military and civilian establishments as to what should be done. It was decided that the government should prepare to immunize the population. Accordingly, Dr. LaMontagne organized manufacturers to produce the vaccine and recruited investigators to field test its immunogenicity and safety. Physicians began to immunize the population.

Unexpectedly, Guillain Barré syndrome appeared in some of the vaccine recipients. Numerous meetings were held to discuss what was going on. The CDC implicated the vaccine itself. The program was suspended. In a subsequent meeting held in the downtown office of the Department of Health and Human Services (HHS), Dr. LaMontagne and I heard Secretary Joe Califano dismiss Dr. David Sencer as director of CDC in the open meeting, a rather brutal conclusion. Dr. LaMontagne and I escaped to be interviewed by Roger Neustadt and Harvey Fineberg who co-authored the book *The Epidemic That Never Was, Policy Making and the Swine Flu Scare*. I understand that a new look is now being taken at the Guillain Barré data.

I had many adventures with influenza before swine flu came along. To tell you about them, I need to give you a little information about my career. When I returned to finish my residency at Boston City Hospital, after three years as a Navy medical officer, one of my attending physicians was Dr. John Dingle, a member of the Thorndike Laboratory with Dr. Maxwell Finland. He earlier had shown that pigeons are a reservoir for Eastern equine encephalomyelitis and had studied outbreaks of meningitis and diphtheria at Halifax, Nova Scotia with Dr. Lewis Thomas.

During the war, Dr. Dingle had been director of the laboratory of the Commission of Acute Respiratory Diseases (CARD) based at Fort Bragg, North Carolina. When he went to Western Reserve University as chairman of a new Department of Preventive Medicine, he brought with him essentially the entire professional staff of the CARD group. He asked me to join him as a fellow. My assignment was to run the Infectious Diseases Division housed in a recently remodeled special unit of Lakeside Hospital, part of University Hospital.

CARD was one of a number of special commissions under the Armed Forces Epidemiological Board (AFEB) of the Department of Defense. Because of the impact of pandemic influenza during World War I, early in World War II the Army created a Commission on Influenza under Dr. Thomas Francis of the University of Michigan. His laboratory in the School of Public Health was already busy studying influenza viruses.

In the early 1940s, this laboratory produced a crude, whole inactivated virus vaccine that was shown to protect U.S. forces. Dr. Jonas Salk was a member of the staff at Michigan and later used a similar formaldehyde inactivation procedure at Pittsburgh to produce killed polio vaccine, the efficacy of which was demonstrated in the 1954 field trial coordinated by Dr. Francis. Subsequent painstaking and sustained work at Michigan by Dr. H.F. (John) Massab led to the development and testing of a live, attenuated trivalent influenza vaccine by Aviron, a relatively new company.

The vaccine, called FluMist, is administered as a nasal spray using a special applicator. It was shown to be greater than 90 percent effective in field trials coordinated by Dr. Robert Belshe. Aviron was purchased by MedImmune, which then became a partner with Wyeth to promote sale of the new product. Its uptake by physicians and the public in 2003-2004 was disappointing. I postulate that this was for two reasons: (1) the FDA Advisory Committee restricted its use in young children and older adults, the groups most in need of protection; and (2) the industry hoped to sell this spectacular vaccine at too high a price.

Earlier this month, Wyeth and MedImmune severed their partnership for selling FluMist. Under a new agreement, MedImmune will have rights to both FluMist and a next generation vaccine, called CAIV-T. Unlike FluMist, the new vaccine does not have to be frozen. I hope for the commercial success of both vaccines. It would be a shame not to capitalize on our 37 years of efforts to produce and market a live, easily updated influenza vaccine.

The major research focus of the department at Western Reserve was a study of illnesses in the homes of middle class families with children in the neighborhoods adjoining the medical school. Understandably, acute respiratory diseases were found to be the most common cause of illness and resulted in studies of adenoviruses, parainfluenza viruses, and particularly influenza. As a result of Dr. Dingle's connection with the AFEB, I became active with the Commission on Acute Respiratory Diseases and eventually its director.

In the summer of 1957, I was camping with my own young family in a cottage at Woods Pond, Maine, when a call came from the executive director of AFEB. He reported that Dr. Thomas Francis had returned from Japan with a new Influenza A virus that threatened to be the cause of the next epidemic. It had been decided that a group should seek a site in South America where the disease was expected to strike first to find a suitable place to put in a research group to learn about the disease.

As a result, I went to South America as a member of a team composed of Dr. John Seal, then still a captain in the Navy, Dr. Keith Jensen of Dr. Francis' laboratory, and Dr. Akoura Senz representing PAHO, and serving as our interpreter. In Santiago we were joined by Manual Ogonno of the Chile National Health Service. We started in Caracas, Venezuela, touched down at São Paulo and Rio de Janeiro, Brazil, on to Montevideo, then across the mountains to Santiago. We selected Santiago as the best site, and departed. The first case of Asian influenza occurred on a naval vessel in Valparaiso the day we left.

At a Santiago hospital, we found an entire ward full of patients with typhoid, and were told that chloramphenicol was ordered by the ton. Of note is that the typhoid Ty21a vaccine studies, later undertaken with care by Dr. Myron Levine, were conducted in Santiago and its environs.

In the early 1950s, we experienced the repeat occurrence of influenza epidemics in the families, and thus were prepared to reactivate the family study, which was about to be shut down when Asian influenza came along. I learned much about the epidemiology of influenza. After I left the Division of Microbiology and Infectious

Diseases (DMID), I was privileged to attend a number of meetings related to that subject. In particular, these involved planning for the next pandemic. There were a great number of these meetings attended by individuals who contributed their time and talent to developing such a plan. Dr. Peter Patriarca of the FDA produced a number of drafts. The Office of the Secretary of HHS has yet to accept and approve a pandemic plan for the United States, but the prospects for such an approval have greatly improved with the intervention of a reenergized National Vaccine Program Office. Its publication of the plan should offer a model to those concerned with biodefense.

Polio

I now invite you to join me in the section of Vaccine Land devoted to poliomyelitis, the subject of Dr. Sam Katz's address last year.

My clinical introduction to polio occurred in the summer and fall of 1952 when the Cleveland metropolitan area experienced the highest incidence of polio in its history. The virus most frequently isolated from patients was Type 1. These cases flooded Lakeside Hospital, and Cleveland City Hospital. At Lakeside, I became chairman of the Polio Committee and rapidly learned of the indications for tracheostomy and about Sister Kenny's hot packs. The community ran out of respirators for a while, and required help from the National Foundation for Poliomyelitis. Only one paralytic case of Type 1 occurred in a 13-year old boy in one of our study families. He recovered without residual.

Two years later, during the months of October and November 1954, at which time no paralytic poliomyelitis had been reported, 16 Type 1 polioviruses were isolated from pharyngeal swabs collected in response to respiratory illness in three families. The individuals who shed virus had no serologic evidence of previous infection. In the search for avirulent strains for use in live virus vaccines, two isolates were sent to Dr. Albert Sabin for testing in monkeys. He summarized the results as follows: "The quantitative tests . . . performed in monkeys . . . indicate that they belong at the attenuated end of the spectrum that could be expected to be nonparalytogenic for chimpanzees in the maximum dosage." Later, I visited Dr. Sabin at his laboratory at Jones Hospital in Cincinnati with a request that paired sera from patients with non-bacterial gastroenteritis be tested with a virus he called a human enteric virus. The virus was later classified as a reovirus. The serologic tests were negative. However, during my visit to Dr. Sabin's laboratory I was privileged to review his protocols for testing polio

strains in monkeys. It was a great privilege to see the questions addressed in his studies and to note the evidence he required before accepting viruses for his vaccine.

One of the investigators in Dr. Sabin's laboratory at the time was a scientist who later joined NIAID, Dr. Robert Chanock. He had just discovered parainfluenza virus. We will speak more of him later.

There were great moments in polio vaccinology. The list would begin with studies of the disease and the growth of the virus by Drs. Thomas Weller and Frederick Robbins, working with Dr. John Enders. Incidentally, Dr. Enders was a laboratory instructor of mine who later helped Dr. Sam Katz with the isolation and identification of measles virus, making possible the highly effective measles vaccine.

The trivalent polio vaccine developed by Dr. Sabin was attenuated, grew in the gut, and spread to others, increasing the number of immunized. After my move from Cleveland to Charlottesville, I was delighted to be part of a group that delivered live trivalent oral vaccine to the citizens of Virginia on days for mass immunization labeled "Sabin on Sunday." The vaccine has been highly effective in controlling polio epidemics, and has led almost to the eradication of polio throughout the world. Unfortunately, a few spots remain where it is difficult to achieve mass immunization. Another complication is the appearance of virulent viruses that originated from an attenuated strain in the vaccine. This has led to the use of Dr. Salk's inactivated vaccine in areas of the world where polio has disappeared.

Next, I want to develop lists of great moments in vaccinology for two other vaccines, adenovirus and *Haemophilus influenzae* type B (Hib), to illustrate the continuity of science and how final licensure and distribution are dependent on a lot of scientific steps that go before.

Adenovirus Vaccine

In the early 1940s, Investigators of the Commission on Acute Respiratory Diseases were faced with a mass of undifferentiated respiratory illness at Fort Bragg, North Carolina. Clinically and epidemiologically they identified three diseases: acute respiratory disease of military recruits (ARD), atypical pneumonia, and the common cold. Using human volunteers, drawn from conscientious objectors and housed in isolation at the Carolina Pines Hotel, in Pinehurst, North Carolina, they were able to show by transmission of respiratory

tract secretions and cross challenges that these three syndromes were distinct entities.

Acute respiratory disease of military recruits, as it was called in the beginning, now designated ARD, was the most important respiratory illness at all military training camps. Another decade later during the winter of 1952-1953, Drs. Maurice Hilleman and J.H. Warner isolated an agent from a case labeled "primary atypical pneumonia." The isolate was called RI67. That same year Drs. Wallis Rowe and Robert Huebner of the National Microbiological Institute at NIH reported the isolation of three immunologically distinct agents from human adenoid tissue undergoing degeneration in tissue culture. They were termed adenoid degeneration agents. Later the name was changed to adenovirus. It was shown that the virus isolated by Hilleman was of the same family as the ones isolated by Rowe and Huebner. The first three of their isolates became types 1, 2 and 3; RI 67 became type 4. Many adenovirus serotypes are now known, most of the higher types are from the gastrointestinal tract.

In 1955, Dr. Huebner and his associates prepared a killed type 3 adenovirus vaccine that induced antibody and prevented illness of volunteers challenged with the homologous virus. The next progress was made by Dr. Robert Chanock, now at NIAID, the successor to the Microbiological Institute. He and his NIH investigators, using virus grown in embryonic kidney cell culture, showed that live type 4 and type 7 adenoviruses would selectively infect the lower intestinal tract administered in capsules. The virus did not spread from the lower intestinal tract. Next, investigation of oral adenovirus infection showed that it induced moderately high levels of neutralizing antibody without any signs or symptoms of illness.

A large scale vaccine production of type 4 virus was propagated in human fibroblast cultures. When administered to the volunteers in enteric coated capsules, the virus infected the lower intestinal tract and induced high levels of antibody and did not spread from the volunteers to susceptible contacts. In collaboration with U.S. Navy scientists, Dr. Chanock and his associates used this sequence to test adenovirus vaccine. They had observed that adenovirus infections were infrequent in recruits during their basic training at Marine Recruit Depot at Parris Island, South Carolina, but caused epidemics when they were transferred to Camp Lejeune, North Carolina for additional training. The vaccine was found to be very effective.

Subsequent studies at Fort Dix noted that the suppression of type 4 virus by type 4 vaccine fostered the emergence of type 7 virus in the

immunized population. Consequently, a bivalent vaccine was developed. When administered to trainees at Fort Dix in 1969 during an outbreak of ARD, the rate of ARD associated with type 7 antiviral was reduced by 96 percent and no decrease of immunogenicity of type 4 vaccine was evident.

The following year, Wyeth Laboratories, guided by Dr. Ben Ruben, the man who developed the bifurcated needle to deliver standard doses of smallpox vaccine, replaced the capsules with enteric coated tablets. Bivalent vaccine was then given to all recruits at Fort Dix and Fort Leonard Wood, and later to all Army recruits by fiscal year 1971. It was estimated that the vaccine prevented nearly 27,000 hospitalizations saving \$7.53 million at a cost of \$4.83 million.

In 1973, over 25 years since the disease was first recognized, the AFEB recommended that vaccine containing both types 4 and 7 adenovirus be administered routinely to all military training personnel. The Army contracted with Wyeth to continue to produce the vaccine. The vaccine continued to control acute upper respiratory diseases and pneumonia among military trainees. Unfortunately, this was not to last. In 1995, the sole manufacturer, Wyeth, ceased production. The drug company had requested funds from the Department of Defense to upgrade its production facility to meet good manufacturing practice standards. Unfortunately, the then occupant of the position of Assistant Secretary of Defense, Health Affairs, apparently ignorant of all the history that had gone before, failed to approve the expenditure. In September 2000, Gregory C. Gray and six co-authors, representing “The Adenovirus Surveillance Group” published a paper in *Clinical Infectious Diseases* reporting that ARD was again causing military disease epidemics. This paper was accompanied by an editorial by Dr. Sam Katz.

Later, retired General Philip Russell wrote letters supporting the resumption of adenovirus immunization. Continued surveillance by the military demonstrated that, as predicted, adenovirus type 4 and 7 disease had returned, interfering with basic training schedules. As is true with all vaccines, an unused vaccine will not work. I am pleased to report that in the year following Dr. Gray’s report (2001), DOD signed a contract with BarriLabs to produce a six valent (types 4 and 7) vaccine for the military. Phase III trials are to start in 2004 with FDA approval anticipated in 2008.



I would like to pause now to pay tribute to the many virologists and technologists who perfected cell culture and other procedures, such as electromicroscopy, that allowed us to grow, measure and see viruses. Just think of the live virus vaccines we now have—measles, mumps, rubella, varicella, polio, yellow fever, that would not exist had not these investigators persisted. Hopefully, NIH can continue to provide federal funds to support current investigators with good ideas who seek to cultivate and produce vaccines for other viral diseases. Some viruses still challenging vaccine development have already been identified; these include HIV, dengue, Ebola virus, West Nile, respiratory syncytial, SARS, and further attenuated smallpox.

We have arrived at the bacterial section of Vaccine Land, an expansive area. Over in a historic corner are two remarkably successful toxoids that continue to protect against two bacterial toxins—diphtheria and tetanus. These proteins have recently found a new use in the design of polysaccharide (PS) vaccines, because when conjugated with PS, they convert the PS antigen from a T-cell independent one to a T-cell dependent one that is much more effective in young children. This section of my presentation might properly be titled, “Polysaccharide Vaccines, Plain and Conjugate.”

To further emphasize the achievements of our profession, I will now provide my perspectives of the development vaccines for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib).

Pneumococcal Vaccine

The story begins with the identification in 1917 by Dochez and Avery of the specific soluble substance elaborated by the *pneumococcus*, and subsequent studies of the substance by Avery and Heidelberger. In 1927, Schiemann and Casper demonstrated that the substance was immunogenic in the mouse. Three years later, Francis and Tillett reported the induction of antibodies in humans. The protective polysaccharide antigen had been identified.

A number of vaccine trials followed, the largest being one of a bivalent (types 1 and 2) vaccine given to more than 40,000 males in the Civilian Conservation Corps in the late 1930s. The results were inconclusive. During World War II, pneumococcal pneumonia became a problem at an Army air base in Sioux Falls, South Dakota. Fortunately, Dr. Heidelberger had continued his studies and was able to provide purified type-specific vaccines for the predominant types identified by a carrier

survey. This classic study demonstrated that immunization of humans with type-specific capsular polysaccharides of selected pneumococcal types (1, 2, 5, and 7) was effective in preventing pneumonia caused by those types. Of equal interest was the observation that immunizing 50 percent of the population greatly reduced in nonimmunized subjects the incidence of pneumonia caused by the vaccine types.

E. R. Squibb and Sons then developed and marketed two six-valent pneumococcal capsular polysaccharide vaccines, one vaccine for use in adults, the other for use in children. These vaccines never gained widespread acceptance. Physicians in the early 1950s chose to rely on new antimicrobial agents to treat bacterial pneumonia, rather than on prevention through immunization. In 1954, therefore, Squibb terminated its production of pneumococcal vaccine. The Biologics Control Laboratory of the National Microbiological Institute, National Institutes of Health, withdrew without prejudice Squibb's license to produce these vaccines, and Squibb subsequently abandoned all of its pneumococcal vaccine research and development programs.

Perception of the need for the development of a pneumococcal polysaccharide vaccine generally diminished until Dr. Robert Austrian produced data showing that despite antibiotic treatment, the mortality rate for bacteremic pneumococcal pneumonia was still high. In 1967, the Infectious Diseases Advisory Committees of the National Institute of Allergy and Infectious Diseases (NIAID), of which I had just become a member, recommended to Dr. Dorland Davis, the institute's director, that funds be provided for the research and development of pneumococcal vaccine. NIAID contracted with Eli Lilly and Company to develop an experimental polyvalent polysaccharide vaccine to be tested by Dr. Robert Austrian and other investigators. In 1976, 13 years after his first report to the Association of American Physicians, Austrian informed that group of the convincing results obtained in a population of novice gold miners in South Africa.

Just as Eli Lilly's vaccine was being shown to be effective in South Africa, the company made a corporate decision in 1975 to stop producing it. Fortunately, Merck Sharp & Dohme intensified its efforts to develop a pneumococcal vaccine. Merck, with Dr. Maurice Hilleman leading its vaccine program, had committed itself earlier to the task of developing and producing a meningococcal polysaccharide vaccine for the Army. Merck conducted independent clinical trials among gold miners in South Africa and obtained levels of safety and efficacy comparable to those found by Austrian with

the product produced by Eli Lilly. Merck applied to the Food and Drug Administration (FDA) in 1976 for a license to manufacture and market a 14-valent vaccine.

The company was issued a product license on November 21, 1977, and began marketing PNEUMOVAX® in February 1978. Lederle Laboratories obtained a product license for its 14-valent vaccine in August 1979 and began marketing PNU-IMMUNE® shortly thereafter. Subsequently, 23-valent vaccines were developed and licensed in 1983. They contain 87 percent of the serotypes responsible for bacteremic pneumococcal disease in adults worldwide, and are reported to be 65 to 70 percent effective in healthy adults.

Haemophilus influenzae type b

Now, consider *Haemophilus influenzae* type b (Hib). In the first half of the last century, 16,000 to 25,000 children in the United States developed infections caused by Hib each year. Bacterial meningitis, the most serious complication of Hib disease, occurred in 60 percent of affected children. Ten percent of these children died, while many survivors suffered serious and permanent disabilities. Other infections included bacteremia, pneumonia, empyema, pericarditis, cellulitis, septic arthritis, and epiglottitis.

When I was a medical student taking microbiology, Dr. Leroy Fothergill, one of my professors, offered an elective course in immunology, then an infant science. He and his colleague, J. Wright, reported that the disease occurred as the “bactericidal power of blood” against Hib declined with the advancing age of the children. In that same year, Dr Margaret Pittman reported on the action of type specific Hib antiserum. Antibodies were clearly important. How best to induce them? The polysaccharide of Hib, a polyribose phosphate (PRP), and other bacterial T-cell independent polysaccharides are poorly immunogenic in the young, particularly those less than 2 years of age.

Fortunately, Drs. John Robbins and Rachel Schneerson of NICHD reported that coupling proteins such as diphtheria and tetanus toxoids to Hib polysaccharides greatly enhanced their immunogenicity for young children. Industry responded to this discovery by producing five different Hib conjugate vaccines: each with a different protein. They are listed in *The Jordan Report*.

The impact of the vaccines has been dramatic. There has been significant reduction of incidence of Hib invasive disease in immunized children throughout the world. It was most gratifying to see this pictured

on the cover of the 1998 *Jordan Report* for the U.S., U.K., Australia and Uruguay. The disease has been eliminated without eradicating the organism.

After the success of the Hib polysaccharide-protein conjugate championed by Robbins and Schneerson, steps were taken to apply this approach to the development of a pneumococcal vaccine for children. In 1987, NIAID sought the interest of industry in manufacturing a heptavalent conjugate vaccine. Only one company, Praxis Biologics, a new venture started by Dr. Richard Smith, Professor of Pediatrics at the University of Rochester and a close associate of NIAID grantee Dr. Porter Anderson, an expert on polysaccharides, submitted a contract proposal.

Combining pneumococcal conjugates was not easy. It took time going from three, to five, and to seven serotypes, trying different proteins, and conducting Phase I trials during years when Praxis was absorbed by Wyeth-Lederle Vaccines. Finally, in 2000, 21 years after the first 14-valent polysaccharide vaccine was licensed, a heptavalent conjugate vaccine was licensed. This contains the most common serotypes that cause acute otitis media (4, 6B, 9V, 14, 18C, 19F, and 23Y) conjugated to the nontoxic diphtheria toxin analogue CRM197. Two efficacy trials, one in California and the other in Finland, have shown the vaccine to be safe and moderately effective in the prevention of otitis media caused by serotypes included in the vaccine, but the Finnish trial demonstrated an increase in the incidence of otitis media from serotypes not in the vaccine. Merck has been expected to submit a license application for its multivalent conjugate.

Bureaucrats and Bureaucracy

It is time to step back through the looking glass and leave the wonders of Vaccine Land for the realities of the real world. I will conclude with a brief account of my contribution to the federal bureaucracy.

Some months before I turned over responsibility for the Program for the Acceleration of Vaccine Development that Dr. John Seal and I started, a group of vaccinologists began to agitate for the notion of a national office for the coordination of all vaccine program by NIH, CDC, FDA, DOD, and industry. The group succeeded, and HHS began to develop legislation for the creation of such an office. Dr. Alan Hinman and I conspired to have the resulting bill call for the effort to be directed by the Assistant Secretary of Health, then Dr. James Mason. A National Vaccine Program Office (NVPO) was created to manage day-to-day activities, under its own director.

Dr. Anthony Robbins became the first director of this office located at HHS headquarters in the Humphrey Building. Members of the first staff included Drs. D. A. Henderson and Roy Widdus. I was invited to join the group as a part time consultant. Fortunately, Dr. Fauci had allowed me to continue within DMID as a volunteer, permitting me to keep in touch with vaccine research. The embryonic group barely had time to appoint the first multidisciplinary National Vaccine Advisory Committee (NVAC), called for by the legislation before the office was moved to the Parklawn Building under Dr. Kenneth Bart. New staff members were recruited; the office space was remodeled. Things were moving along. I wrote a position paper calling for a better BCG that was endorsed by Dr. Barry Bloom; I would like to think it had in some way fostered the generosity of the Gates Foundation in support of tuberculosis research.

Then, with little warning, the new offices had to be abandoned. Senator Dale Bumpers, a strong supporter of immunization and a powerful member of the budget committee, had the funds for NVPO transferred to CDC. At CDC, Dr. Martin Myers was put in charge of the NVPO. He came to realize that it needed the strong control and authority initially visualized. The NVPO is back in Washington under the informed leadership of Dr. Bruce Gellin. I hope that it will be adequately staffed to contribute to the defense of bioterrorism and homeland security.

Now to the bureaucrats. When I became a federal employee in 1976, it was not unlike being a department chairman or a medical school dean. It all depends on the quality of those you are working with. My colleagues at NIAID were and are of high quality, and a pleasure to work with. Our program officers were as interested in the success of R01 and program project grants, and of contracts, as the investigators and contractors themselves. They are responsible for most of the contents of *The Jordan Report*. They are true professionals and should not be out-sourced.



Thank you for your attention, and for inviting me to join such a distinguished group of predecessors. I hope you will agree that Vaccine Land is truly a Wonderland populated by some very talented people. I hope you have a little better understanding of how NIAID fosters vaccine research and development.

THE ALBERT B. SABIN GOLD MEDAL

The Albert B. Sabin Vaccine Institute annually recognizes and honors those who have made extraordinary contributions to the field of vaccinology by awarding the Albert B. Sabin Gold Medal.

PAST HONOREES

Donald A. Henderson, M.D., M.P.H., 1994 · Robert M. Chanock, M.D., 1995
Joseph L. Melnick, Ph.D., 1996 (*d. 2001*) · Maurice R. Hilleman, Ph.D., D.Sc., 1997



1994



1995



1996



1997

Myron M. Levine, M.D., D.T.P.H., 1998 · Allen C. Steere, M.D., 1998
Maj. Gen. Philip K. Russell, MD. (USA Ret.), 1999



1998



1998



1999

Ciro A. de Quadros, M.D., M.P.H., 2000 · John B. Robbins, M.D., 2001
Stanley A. Plotkin, M.D., 2002 · Samuel L. Katz, M.D., 2003



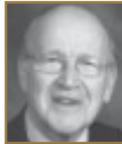
2000



2001



2002



2003

ALBERT B. SABIN VACCINE INSTITUTE

The Albert B. Sabin Vaccine Institute, founded in 1993, is a non-profit organization committed to Dr. Sabin's global health vision. Like the late vaccine pioneer and humanitarian, the Institute strives to save lives by advancing new vaccine developments and increasing global immunization. This mission is based on a fundamental premise: vaccines are the most humane and effective form of medical intervention ever devised. By advocating the integration of scientific advances and public policy, the Institute recognizes the enormous potential for vaccines to save lives, prevent suffering, and reduce global health care costs attributable to disease.

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