

PORTRAIT



## Portrait of an ISV fellow

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I am a child of the Bronx, a milieu that produced many hard-working and accomplished people from an emerging middle class before World War II, mainly of Irish, Italian or Jewish origin, who flourished in the competitive atmosphere of New York City. My father was a commercial telegrapher, talented with his hands and adept at fixing things. Although he suffered joblessness during the depression of 1929 and was reduced to digging ditches, he ended his career as head of communications in a Wall Street stock brokerage company. My mother was much more than a housewife: she was endlessly and continuously active in community affairs and in my schools' parents associations. As a speaker, she could extemporize on any occasion.

My father taught me to read at age 3, and I made money for a cousin who bet his friends that I could read the New York Times. However, it is worth mentioning that I had three diseases that are now vaccine preventable before reaching the age of 10 years: pertussis, pneumococcal pneumonia, and severe influenza. Despite that, I was able to skip grades in elementary school and to enter high school at age 12. Indeed, the defining experience of my life was entry into the Bronx High School of Science. Certainly it was the most challenging intellectual atmosphere I have ever experienced, as the teachers and the students were far above average. While I was at Bronx Science, at age 15, I read two books that set me on the course of my life: *Microbe Hunters* by Paul De Kruif and *Arrowsmith* by Sinclair Lewis. Regrettably, neither is popular today, but they should be. *Microbe Hunters* contains pocket biographies of famous microbiologists and *Arrowsmith* is a novel about a physician who becomes an epidemic sleuth and a vaccine developer. I can say that after reading those two books there was never a doubt in my mind as to my choice of a future career.

From high school I entered New York University. There I majored in biology and was able to become a laboratory assistant to Professor Hall, a microbiologist. At the end of my college years I was uncertain as to whether to enter graduate school or medical school, a decision that was made for me when I won a New York State scholarship to the latter. This was more than fortunate, because my parents could not have afforded to pay for medical school. I entered Downstate Medical School in Brooklyn in 1952. In my last year there Dr. Robert Austrian of pneumococcal fame took me into his laboratory, where I worked on *Pseudomonas* infections. Although I dabbled with several medical specialties, I soon decided that Pediatrics was the specialty closest to my ambitions, and after graduation sought an internship at Cleveland

Metropolitan Hospital, where Fred Robbins, who had shared a Nobel Prize for cell culture of viruses, was head of Pediatrics. There I underwent the baptism by fire common to interns at a large city hospital, but I did also get some experience in Robbins's laboratory.

At that time there was still a military draft and I had always wanted to learn how to fly, so I joined the Air Force. However, before finishing internship another young man in Robbins's lab told me about the Epidemic Intelligence Service at the Centers for Disease Control. I applied to EIS and was accepted, so I resigned from the Air Force. Soon I was in Atlanta, learning about epidemiology of infectious diseases. At the end of the EIS training course Alexander Langmuir gave us a list of potential postings to choose from, subject to his agreement. By that time I was perusing the virological literature, including interesting and charmingly written articles by someone named Hilary Koprowski. Then I learned, I don't remember how, that Koprowski was soon to become Director of the Wistar Institute at the University of Pennsylvania in Philadelphia. By sheer coincidence, one of the EIS assignments on offer was to an anthrax laboratory at the Wistar. The anthrax unit was at Wistar because factories in Philadelphia were making linings for men's suits using goat hair imported from India and Pakistan. Unsurprisingly, the shipments included hair from animals dead from anthrax, which therefore were often contaminated with anthrax spores. Although I had no particular interest in anthrax, I reasoned that if I came to Wistar I might be able to obtain entrance into Koprowski's virology laboratory.

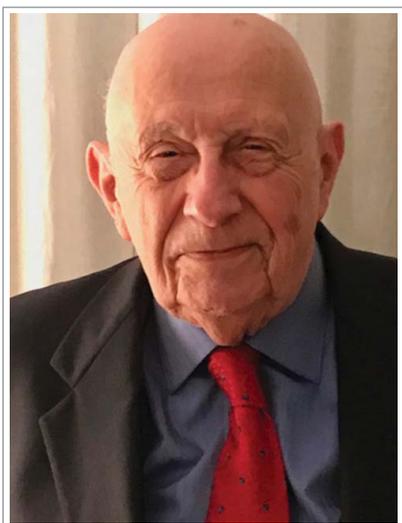
At that time, Philadelphia was considered to be an unattractive place, but to the surprise of Langmuir, I campaigned for the Wistar post, and indeed succeeded in being assigned to the anthrax lab. Lo and behold, shortly after I arrived at Wistar, a pathologist called from New Hampshire to report a case of inhalation anthrax. Indeed, when I went to Manchester to investigate I found that there were five cases, including four deaths, which I traced to the importation of a highly contaminated lot of goat hair. The US Army at that time was in the midst of a placebo-controlled study of a new anthrax vaccine, in which some of the workers at the factory in question had been enrolled. So in the end I was able to write several papers on anthrax and anthrax vaccine, one of which was republished at the time of the 2001 anthrax attacks.

But I had not forgotten my motive to come to Wistar, so one day I entered Koprowski's office to ask if I could train in his poliovirus laboratory. He readily acquiesced, and soon I was

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#### About Stanley Plotkin.

Dr. Plotkin is Emeritus Professor of the University of Pennsylvania, and Adjunct Professor of the Johns Hopkins University. Until 1991, he was Professor of Pediatrics and Microbiology at the University of Pennsylvania, Professor of Virology at the Wistar Institute and at the same time, Director of Infectious Diseases and Senior Physician at the Children's Hospital of Philadelphia. He maintained laboratories at both CHOP and Wistar. In 1991, Dr. Plotkin left the University to join the vaccine manufacturer, Pasteur-Mérieux-Connaught (now called Sanofi Pasteur), where for seven years he was Medical and Scientific Director, based at Marnes-la-Coquette, outside Paris. He left France in 1998, and is now consultant to many vaccine manufacturers, biotechnology companies and non-profit research organizations as principal of Vaxconsult. He also continues to teach at the University of Pennsylvania.

Dr. Plotkin attended New York University, where he received a B.A. degree, and then the State University of New York Medical School in Brooklyn, where he received an M.D. degree in 1956. His subsequent career included internship at Cleveland Metropolitan General Hospital under Fred Robbins, residency in pediatrics at the Children's Hospital of Philadelphia and the Hospital for Sick Children in London and three years in the Epidemic Intelligence Service of the Centers for Disease Control of the US Public Health Service. While in EIS in the 1950s he worked on the development of oral polio vaccine and on the efficacy of a vaccine against inhalation and cutaneous anthrax.

He has been chairman of both the Infectious Diseases Committee and the AIDS Task Force of the American Academy of Pediatrics, liaison member of the Advisory Committee on Immunization Practices and Chairman of the Microbiology and Infectious Diseases Research Committee of the National Institutes of Health. Dr. Plotkin received the Bruce Medal in Preventive Medicine of the American College of Physicians, the Distinguished Physician Award of the Pediatric Infectious Diseases Society, the Clinical Virology Award of the Pan American Society for Clinical Virology, the Richard Day Master Teacher in Pediatrics Award of the Alumni Association of New York Downstate Medical College, and the Marshall Award of the European Society for Pediatric Infectious Diseases. In June 1998, he received the French Legion of Honor Medal; in June 2001, the Distinguished Alumnus Award of the Children's Hospital of Philadelphia, in September 2006 the gold medal from the same hospital; the Sabin Gold Medal in May 2002, in September 2004 the Fleming (Bristol) Award of the Infectious Diseases Society of America, in May 2007 the medal of the Fondation Mérieux, in 2009 the Finland Award of the National Foundation for Infectious Diseases and the Hilleman Award of the American Society for Microbiology, and in 2013 the Career Achievement Award from the Association for Clinical and Translational Medicine, as well as the Caspar Wistar Medal of the Wistar Institute of Biological Research. In 2014 he received the Charles Mérieux Award of the National Foundation for Infectious Diseases and the Sheikh Hamdan (Dubai) Award for Medical Sciences. He was elected to the Institute of Medicine of the National Academy of Sciences in 2005, to the French Academy of Medicine in 2007, to the French Academy of Pharmacy in 2013, and to the Thai Pediatric Infectious Diseases Society in 2015. Dr. Plotkin is the Founder and a Fellow of the Pediatric Infectious Diseases Society. He is also a Fellow of the Infectious Diseases Society of America, of the International Society for Vaccines, the American Academy of Pediatrics and the College of Physicians of Philadelphia. Dr. Plotkin holds honorary doctoral degrees from the University of Rouen (France) and the Complutense University of Madrid (Spain). He is on the board of the Rostropovich Foundation. Named lectures in his honor have been established at the Pediatric Academic Societies annual meeting, at the International Advanced Vaccinology Course in Anney, France, and at the DNA Vaccines Society. A professorship in his name was established at the Children's Hospital of Philadelphia. His bibliography includes over 800 articles and he has edited several books including the standard textbook

on vaccines, now in its 7th edition and now titled "Plotkin's Vaccines." In 2000, Plotkin proposed and helped organize an Advanced Course in Vaccinology at the Fondation Mérieux, now in its 19th year. In 2015, in the *New England Journal of Medicine*, he proposed an international fund for development of vaccines against emerging diseases, which now exists as the Coalition for Epidemic Preparedness and Innovation. He developed the rubella vaccine now in standard use throughout the world, is codeveloper of the pentavalent rotavirus vaccine, and has worked extensively on the laboratory development and application of other vaccines including anthrax, oral polio, rabies, varicella, pertussis, Lyme disease and cytomegalovirus.

doing at least as much virology as bacteriology and I was like a kid in a candy shop. Koprowski was a fascinating and dynamic leader. He ran the Wistar as his fiefdom, but the great thing was that he allowed no metaphorical walls between investigators and that he often had excellent ideas. Moreover, he was a connoisseur of art and music and could speak several languages. The Wistar scientific staff was international and the jest was that the common language was broken English. By 1959 I was well versed in virology and enjoying myself to the highest degree. The moral of this is that it is far better to be lucky than smart: my coming to Wistar set the course for the rest of my life.

The focus of Koprowski's lab was polio, as he was in competition with Albert Sabin to develop an oral vaccine. There I learned about attenuation of live viruses and was a participant in the running battle between the two giants to attain a licensed vaccine. Meeting Sabin, Salk and other famous scientists at conferences or other occasions was great fun for a youngster like me. Ultimately, Sabin won the race for a licensed vaccine because the neurovirulence in monkeys of Sabin's strains was less than those of Koprowski, and the race was decided on that ground by the predecessor of the FDA. However, before the competition ended I was sent to the then Belgian Congo in 1959 to collect data on the use of the Koprowski type 1 vaccine strain in large populations.

To say that my visit to the Congo was interesting is to understate. It was my first trip overseas, in an environment that varied from an admirable medical organization to Heart of Darkness chaos. Say what you will about colonialism, the Belgians had done a good job with the polio vaccine studies and there was even a chimpanzee colony for primate studies in what was then called Stanleyville, now Kisangani. Unfortunately, my experience in the Congo came back to haunt me in 1999, when a British journalist published a book which postulated that HIV had been transferred from chimpanzees to humans via Koprowski's type 1 oral polio vaccine, which the journalist alleged had been manufactured in chimpanzee cells. I spent many months searching old records and obtaining vaccine samples to disprove this scurrilous accusation. As my readers will know, other labs have since determined that SIV mutated to HIV in the Cameroon and was transferred from chimpanzees to humans in the 1920s.

After several years at Wistar, I decided that I needed to obtain pediatric credentials, so I left for residencies at Children's Hospital of Philadelphia and the Hospital for Sick Children in London. Before leaving, I obtained from Koprowski the promise of my own laboratory when I returned to Wistar, this time to work on rubella. The risk of rubella to the unborn fetus had been recognized years earlier, and both Tom Weller in Boston and workers at the Center for Biologics (now the FDA) were

finding ways to cultivate rubella virus in cell culture. By coincidence, a rubella outbreak started in Europe in 1963 and spread to the US in 1964–65, leading to a major outbreak that resulted in thousands of damaged infants. Soon after my return to Wistar in 1963 there was plenty of clinical material and I became immersed in diagnosis of acquired and congenital rubella.

However, my intention was always to develop a rubella vaccine. By coincidence Leonard Hayflick and Paul Moorhead at Wistar were studying cultures of fibroblasts from aborted normal fetuses. It soon became clear that those cells could be used to cultivate viruses, and that they were clean of any contaminants such as those that were often present in cells from monkeys and other animals. So I decided to try to attenuate rubella virus in human fibroblast cell strains, using methods I had learned working with polio virus. The strain of rubella I chose was cultured from a fetus aborted because of maternal rubella. I believed that it was less likely that there were unknown contaminants in the uterine environment than in strains isolated from the nasopharynx. Between 1964 and 1969 I succeeded in developing a vaccine strain that was attenuated but immunogenic in humans by injection or intranasal administration.

But I was not the only one developing attenuated rubella viruses. A strain attenuated in monkey kidney cells was developed at the Center for Biologics licensing agency, and a strain attenuated in rabbit kidney cells was developed at SmithKline. In 1969, a large meeting on rubella vaccines was held at NIH, where the three candidate vaccines were presented. Albert Sabin was there, and towards the end of the meeting he rose to say that there was a danger that the human cells I had used contained a cancer-causing virus. Being young and undaunted, I raced to the podium to denounce Sabin for having no evidence for his statements, that he was postulating the presence of ghosts, and to argue that if anything the RA27/3 strain was less likely to be contaminated than the other vaccine strains. There was great applause from the audience following my denunciation. Sabin took my brash remarks quite well and we were subsequently on good terms. Nevertheless, the monkey kidney and rabbit kidney vaccine strains were soon licensed in the US by Merck and SmithKline, while the human cell strain was licensed only in Europe, where the views regarding safety were reversed, in that the human cells were considered safer.

About seven or eight years later, in the 1970s, I received a call from Maurice Hilleman, asking that the RA27/3 strain be made available to Merck. It seemed that others, notably Dorothy Horstmann at Yale, who had tested the several rubella vaccines, had found that the RA27/3 strain produced the best immunogenicity, the best protection against wild virus infection, and good safety. Merck licensed the RA27/3 strain in 1979, and soon it was in use throughout the world, including in the vaccine made by what is now GlaxoSmithKline.

Going back to my days at Wistar, I also worked with Tad Wiktor and Hilary Koprowski on rabies vaccine made in human cell culture. Up to the 1970s the available rabies vaccines required as much as 21 doses and were made in cells that elicited side reactions when administered. The human cell vaccine could be given in 3 to 5 doses and was much more immunogenic. To validate safety and immunogenicity I made a tour of veterinary schools to vaccinate students, which led me to rural areas that I never wanted to see in the first place!

Early in the 1970s there was another change in my life: I moved to Children's Hospital of Philadelphia, where I became Director of the Division of Infectious Diseases, while keeping a lab at Wistar. By the 1980s it became evident to me that vaccinology was a growing field but there was no textbook on the subject. With the late Ted Mortimer I put together the first edition of the textbook *Vaccines* in 1988. The book is now in its 7th edition, produced with the help of co-editors Walt Orenstein, Paul Offit and Kathy Edwards.

Also in the mid-80s it became apparent that rotaviruses are the principal cause of infantile gastroenteritis and therefore a number of laboratories, in particular Albert Kapikian's at NIH, began vaccine development. I obtained a grant from what was then called Institut Mérieux to also work on rotavirus vaccine. I recruited to that task Fred Clark, who had been working on rabies at Wistar, and Paul Offit, whom I put on staff after a very successful fellowship in infectious diseases. When the Institut Mérieux eventually lost interest in rotavirus, we entered a long collaboration with Merck, which almost came to a halt when the NIH vaccine was licensed in August 1998. However, numerous cases of intussusception began to be seen after vaccination with the NIH vaccine, which was withdrawn in October 1999. Offit managed to convince Merck to continue development of our vaccine, which contained five different human-bovine reassortant strains. The pentavalent vaccine was eventually licensed under the name RotaTeq and together with a monovalent rotavirus vaccine developed elsewhere has been remarkably successful in reducing the incidence of rotavirus disease and its attendant mortality and morbidity. It was another lesson that one should not give up easily!

The 1990s were also important in my life because at the beginning of the decade I was offered a chairmanship of a pediatrics department in Los Angeles. I had almost accepted the job when Charles Mérieux and his son Alain came from France and offered me a job as Medical and Scientific Director of the vaccine company they had created: Pasteur-Mérieux-Connaught. I went to Paris and visited the site where I could have my office, a suburb called Marnes la Coquette. After the visit, I was dropped off in central Paris. I was dithering about making a choice between Los Angeles and Paris when I walked across the Pont des Arts between the Louvre and the Institut de France, with Notre Dame and the Tour Eiffel in the distance, and on the spot made my decision to choose Paris!

I spent seven years in Paris and traveled around the world, but the main lesson I learned working for the company now called Sanofi is the difference between academic research and industrial development. When I was an academic I thought that my work was careful, but it was nothing compared to what must be done at a company, where every step must be documented and reproducible, where records must be absolutely complete, and where every decision has major financial consequences.

At age 65 according to French law I could no longer work gainfully, so my wife Susan and I returned to the U.S.A., where I became a consultant to vaccine developers and non-profit organizations. From my office in tranquil Bucks County, Pennsylvania I can communicate all over the world, giving advice that others may or may not take, but it's still fun to give it! I am very much involved in the development of vaccines

against cytomegalovirus, pertussis and Lyme disease, and hope to continue to make contributions to vaccinology. I actually started to work on CMV vaccine in the 1970s and have stayed in the field since then because it is the most important cause of congenital abnormalities. My interest in Lyme disease is to correct the fiasco that led to the withdrawal of an effective vaccine, which because of rising incidence of the disease is needed now more than ever. As is well known, the acellular pertussis vaccines have defects in B and T cell responses that should be corrected to improve their efficacy.

In addition, with others, I was instrumental in launching the new organization called the Coalition for Epidemic Preparedness and Innovation, which seeks to finance the development of vaccines for emerging diseases that do not have a market that is attractive to major manufacturers. As a member of the CEPI Scientific Board I try to promote the development of new vaccines. Also, during the 20 years since my return from France

I have learned how to fly an airplane and how to play the piano! What could be better?

In my college yearbook, now so long ago, I quoted from Tennyson's poem "Ulysses" to signify my ambitions:

"To follow knowledge like a sinking star,  
Beyond the utmost bounds of human thought."

When I graduated college only a handful of vaccines were given to children, based on attenuation or killing of pathogens. Now, at least 16 vaccines are in the routine childhood schedule, and as an example of modern vaccinology the candidate vaccines against cytomegalovirus include DNA plasmids, mRNA, replication defective agents, subunits, vectors and other strategies not contemplated years ago. Thus, at age 86, I prefer to quote lines that appear later in the poem:

"Made weak by time and fate, but strong in will,  
To strive, to seek, to find, and not to yield."