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EDITORIAL

Hilary Koprowski, MD

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Hilary Koprowski, MD, a distinguished and highly respected biomedical researcher, died on April 11, 2013 at the age of 96. Dr. Koprowski was recognized for many achievements, most notably the development of the first oral polio vaccine, but also the generation of the oral rabies vaccine currently used worldwide and for his pioneering work in developing monoclonal antibodies to detect and treat cancer.

A native of Poland, Hilary Koprowski received his MD from Warsaw University. During medical school, he married Irena Grasberg, a physician who achieved scientific eminence for her pioneering work on the development of the "Pap" test. Although not raised religiously, Hilary was of Jewish heritage. Knowing his likely fate had he stayed in Poland, Hilary and Irena left Warsaw in December 1939, a few months after the Nazis invaded Poland.

During the war years, Hilary worked with Ed Lennette, an outstanding virologist at the Rockefeller Foundation in Rio de Janeiro. Together they published classic papers on the pathogenesis of Venezuelan equine encephalitis virus. After the war, the Koprowskis moved to the USA. Hilary was hired by Lederle Laboratories in Pearl River, NY where he began the most important studies of his scientific career.

During the 1940s, Hilary Koprowski was the first scientist to produce attenuated poliovirus by repeated intracerebral passage of poliovirus in cotton rats. His attenuated virus produced immunity in monkeys. He was so convinced that the virus was sufficiently attenuated that he fed it to himself. Afterward, he gave the first live, attenuated poliovirus vaccine to one child in February 1950 and then to 19 more children. Remarkably, none showed any side effects after vaccination, and all of them developed antibodies to the poliovirus. In 1951, Koprowski reported his remarkable findings at a meeting organized by the National Foundation for Infantile Paralysis.

Hilary Koprowski, MD

Afterwards, Howard Howe, a senior polio researcher, remarked: "I think that Dr. Koprowski's data is extremely valuable in giving us a bridge which up to now we have not really had." The manuscript reporting Koprowski's development of the first live, attenuated poliovirus vaccine was published in 1952, years before any papers on polio vaccine development were published by Jonas Salk and Albert Sabin.

Koprowski progressed rapidly with his vaccination studies and organized multiple large clinical trials. By 1957, the efficacy of his vaccine was sufficiently well established to justify the first mass trial of the oral polio vaccine. In 1958, at the invitation of an official of the Belgian Congo, Koprowski's poliovirus vaccine was used to immunize 250,000 children in 6 weeks. None of the children developed polio or any neurological disease, and all produced antibodies to poliovirus. Between1959 and 1960, nine

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million children in Poland were immunized with Koprowski's polio vaccine, virtually halting a polio epidemic there. Among those who recognized the significance of Koprowski's achievement was Albert Sabin, who publically acknowledged Koprowski as the first to develop a live, attenuated oral polio vaccine.

In 1944, Koprowski first became engaged with the rabies problem in the Americas. Joseph Pawan, an eminent pathologist in Trinidad, told Dr. Koprowski about the fight between a vampire bat (a carrier of rabies virus in the Southern Hemisphere) and a fruit-eating bat later found to be rabid. This was almost a prophetic observation of the origin of bat rabies in the USA and Canada decades later. Dr. Harold Johnson, a staff member of the Rockefeller Foundation who specialized in rabies, provided Koprowski with a strain of rabies of human origin which he attenuated by continuous passage in developing chick embryo. This led to the Flury strain vaccine which was eventually used in dogs for life-long immunity after a single inoculation. Koprowski also used anti-rabies antibody in concert with vaccine which successfully protected Persian peasants who were bitten by a rabid wolf.

In 1957, Koprowski became Director of The Wistar Institute of Anatomy and Biology in Philadelphia where he served for 35 years. He was also Professor of Microbiology at the University of Pennsylvania. While conducting his own scientific studies, Koprowski provided remarkable leadership of The Wistar Institute, recruiting outstanding scientists, many from outside the USA. In the 1970s, I remember commenting to Stanley Plotkin that I felt privileged to be a "token American" among such talent. The Wistar Institute never had a large budget and, like many biomedical research institutions (and academic research departments today), endured a "soft money" arrangement. Yet, Hilary kept scientists afloat when their funding lapsed, particularly those who worked hard—he always knew what everyone was doing—and pushed them to eventual success.

During his Directorship, Koprowski continued studies on rabies virus that led to a new vaccine for both humans and animals. With Tadeusz Wiktor and Stanley Plotkin, Koprowski developed the first true modification of the Pasteur vaccine that required only three to four inoculations instead of the 14–21 needed for the standard Pasteur vaccine. The Koprowski tissue culture rabies vaccine is still used today. Koprowski and Wiktor also developed a bait vaccine for foxes based on fusion between rabies antigen and live vaccinia virus that resulted in an almost total eradication of rabies in France and Belgium.

From 1970 to 1980, Koprowski and colleagues conducted ground-breaking work on fusion of somatic cells and unfertilized mouse eggs, including uptake of the heterologous genome by mammalian spermatozoa and transfer to ova through fertilization. From 1978 to 1980, Koprowski and associates developed functional monoclonal antibodies directed against colorectal and pancreatic cancer antigens.

After years of vaccine work on polio and rabies, Koprowski was intrigued by the possibility of a viral cause of multiple sclerosis (MS). From 1971 to 1985, he supervised the Wistar Institute component of a large program project grant at the University of Pennsylvania on the etiopathogenesis of MS, jointly supported by NINDS and the National MS Society. Attempts to isolate a virus involved propagation of cells obtained from more than 24 MS brains and co-cultivation, cell fusion, and inoculation of multiple rodent species and primates. MS brain cells were also "superinfected" with vesicular stomatitis virus to identify a pseudotype virus. Timely examination of cells in these cultures by the neuropathologist, Yuzo Iwasaki, was problematic then, since many Wistar scientists also required access to the single electron microscope. The suggestion to purchase a second instrument was met with Koprowski's "practical" solution of having Iwasaki simply work at night and sleep during the day ("Does the electron microscope know what time it is?") Another example of Koprowski's practical nature was the building of an autopsy room at Ingliss House (a chronic care facility in Philadelphia for patients with advanced MS and other neurological diseases that would not improve) for timely access to MS brain tissue without the need for placement in formaldehyde which otherwise would virtually obviate virus isolation.

After leaving the Wistar Institute, Dr. Koprowski became Head of the Center for Neurovirology at Thomas Jefferson University in Philadelphia and eventually President of Biotechnology Foundation Laboratories, Inc. In the decade before his death, Koprowski directed his efforts toward the development of biomedical products in plants. He succeeded in producing rabies vaccine in spinach and antibodies directed against rabies and cancer antigen in tobacco. In collaboration with Polish scientists, he conducted successful clinical trials with hepatitis B vaccine generated in lettuce.

Dr. Koprowski was the author or coauthor of over 900 scientific publications, reviews, chapters, and books. He was elected to the National Academy of Sciences and the American Academy of Arts and Sciences. He was a Fellow of the College of Physicians of Philadelphia, which in 1959 awarded him its Alvarenga Prize. He served as a consultant to the World Health Organization and the Pan American Health Organization. He held foreign membership in the Yugoslav Academy of Arts and Sciences, the Polish Academy of Sciences, the Russian Academy of Medical Sciences, the Polish Institute of Arts and Sciences of America, and the Finnish Society of Sciences and Letters. Dr. Koprowski received honorary degrees from numerous universities and was the recipient of many honors, including The Order of the Lion from the King of Belgium, the French Order of Merit for Research and Invention, a Fulbright Scholarship, and an appointment as Alexander von Humboldt Professor at the Max Planck Institute in Munich. In 1989, he received both the San Marino Award for Medicine and the Nicolaus Copernicus

Medal of The Polish Academy of Sciences in Warsaw. Dr. Koprowski also received many honors in Philadelphia, including the Philadelphia Cancer Research Award, the John Scott Award, and in 1990, the most prestigious honor of his home city, the Philadelphia Award. In 1995, Dr. Koprowski was awarded the title of "Commander of the Order of the Lion of Finland" by the President of the Republic of Finland. In1997, he was awarded the Legion d'Honneur Award from the French government. In 1998, Dr. Koprowski was presented with the "Great Order of Merit" by the President of Poland, for his polio research. In 2000, Dr. Koprowski was honored with a reception at Thomas Jefferson University to celebrate the 50th anniversary of the first feeding of the oral polio vaccine; at this reception, he received commendations from the US Senate, the Pennsylvania Senate, and Governor Tom Ridge. In 2004, Dr. Koprowski was the recipient of the Pioneer in NeuroVirology award given by the International Society for NeuroVirology for his contributions to the field.

In addition to outstanding professional achievements, there are other memorable aspects of Hilary Koprowski. *Wikipedia* defines "Hilary" as "cheerful" or "merry," descriptors eminently evident in his persona at all times. When he discussed important scientific issues or needed to make decisive financial or other administrative decisions, "HK" or the "Czar," or the "Baron" or merely the "Boss," as many of us affectionately called him, never seemed stressed. A true polyglot with a sophisticated sense of humor, he answered my question about the number of languages he spoke with: "7, none perfect." This helped to explain why, when a fact became clear, one of his favorite expressions was "no certain doubt." When considering alternative possibilities in the "Discussion" section of a paper, he preferred "contrariwise" to "on the other hand." Koprowski was always loyal to his colleagues and associates. His assistant Suzanne Jones, who worked with him for more than 40 years and to whom he referred as the "Boss," had the same respect and genuine affection for Dr. Koprowski as did his professional colleagues. He enjoyed people, good meals, and wine and always offered his guests a fine Cuban cigar after dinner. At his home, various sweets and fruits followed the entree, and just when you thought dessert was finished, Hilary brought out the chocolate because "no meal is complete without chocolate."

Koprowski was also an accomplished pianist. He began private lessons at the age of 6 and continued at the Warsaw Conservatory of Music, even during medical school at the University of Warsaw. In 1940, he graduated from the St. Cecilia Conservatory in Rome, as a student of Carlo Zecchi. When he lived in Rio de Janeiro, he gave solo concerts and taught piano before finding laboratory work with the Rockefeller Foundation. When he moved to Lederle Laboratories, he continued to study piano for four hands at the Turtle Bay Conservatory in New York. During his tenure at The Wistar Institute, he gave annual concerts just before the Christmas holidays for the staff and guests, performing difficult works by Brahms, Schubert, Mendelssohn, Mozart, and Bach in a manner both beautiful and expressive. At the age of 77, he began composing music. He took composition lessons with Richard Wernick at the University of Pennsylvania and traveled monthly to Boston for lessons with Pozzi Escot, Professor at the New England Conservatory of Music. He composed pieces for several instruments and voice, frequently related to poems and/or stories. He produced five CDs of music, with some pieces performed by a Parisian orchestra and some by members of the Philadelphia orchestra at his 85th birthday party and again 5 years later. His compositions were also performed on special occasions at private concerts in Philadelphia and abroad. Several of his compositions have already been published. Among my most cherished possessions is the birthday gift of his composition for unaccompanied violin of well-developed variations of "Hava Nagila."

Besides music, Dr. Koprowski's knowledge of art, literature, and language was amazing. His home contained a "gallery" room filled primarily with Flemish paintings, and other rooms with more than a thousand books, ranging from the classics to detective novels.

Dr. Koprowski's wife of 74 years, Irena, died in 2012. He is survived by two sons, five grandchildren, and three great-grandchildren.

I have never met another person who was equally at home with medicine, science, musical performance and composition, art, literature, and language. In the fullest sense of the word, Hilary Koprowski was the true embodiment of the "cultivated" man. His creativity and work ethic were extraordinary. Thomas Mann said that "genius" is "great intellect" or "hard work." Hilary Koprowski exhibited both. His scientific contributions truly left the world a better place than it was before he entered it. We mourn the passing of a mentor, colleague, and dear friend. We will miss him dearly.

Don Gilden, MD