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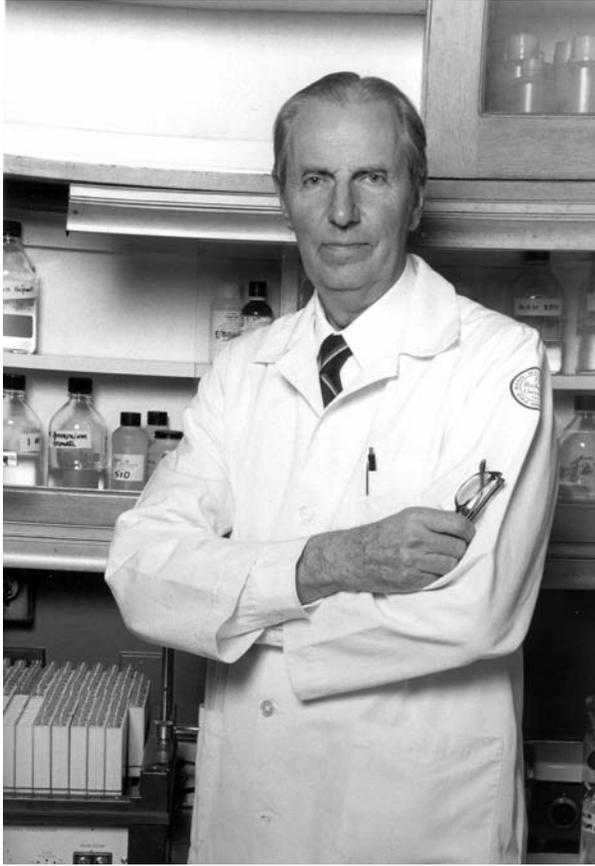
IGOR TAMM
1922—1995

A Biographical Memoir by
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Biographical Memoir

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Igor Tamm

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April 27, 1922–February 6, 1995

BY PURNELL W. CHOPPIN

IGOR TAMM, VIROLOGIST, CELL BIOLOGIST and pioneer in studies of virus replication and the chemical inhibition of such replication, died at the age of 72 on February 6, 1995, at his home in Watch Hill, Rhode Island, of a chronic lung disease that he had battled with characteristic quiet courage and without complaint for over 50 years. He was born on April 27, 1922, in Tapa, Estonia. He attended the State English College in Tallinn, Estonia, from 1939 to 1944 and the Tartu University Medical Faculty in Tartu, Estonia, from 1942 to 1943. His father, an architect, died when Tamm was young. Igor's mother, who came to the United States after him, spent a number of years associated with the American Geographical Society.

As a young boy Tamm had lived under both the German and Soviet occupations of Estonia. In 1943, after the word went out that Estonian teenagers were to be taken into the German army and sent to the Russian front, he and a fellow medical student escaped in a small boat, which they sailed late at night through the German blockade to Finland. Finland was at that time occupied, so they stowed away in the coal storage area of a freighter for several days until it arrived in Sweden. Soon after emerging from the ship, he

developed the first symptoms of the disease from which he would suffer for the rest of his life.

In Stockholm, Tamm entered medical school at the Karolinska Institutet. He had long been interested in going to the United States, and while at the Karolinska, he met an American diplomat, a Yale alumnus, who encouraged him to apply to the Yale Medical School. In 1945 Tamm transferred to Yale, receiving his M.D. with honors in 1947. After two years of house-staff training in internal medicine at the Yale-New Haven Hospital, he moved in 1949 to the Rockefeller Institute for Medical Research, later to become Rockefeller University, which remained his beloved scientific home until his death, and which he graced by his presence for four and a half decades. There he rose to the rank of professor and senior physician in 1964, Abby Rockefeller Mauzé Professor in 1986, and professor emeritus in 1992. In 1959 he became head of the Laboratory of Virology, succeeding his mentor Frank L. Horsfall Jr., who left the Rockefeller Institute to become the director of the Sloan-Kettering Institute for Cancer Research. This transition was very smooth because Horsfall, as vice-president and physician in chief of the hospital, had for several years been increasingly involved in administrative matters, and Tamm was in effect acting as head of the laboratory and primary mentor of the younger people there.

While at Yale Medical School, Tamm met a classmate, Olive E. Pitkin of Bennington, Vermont. They were married in 1953. Olive, a highly talented pediatrician, spent many years with the New York City Department of Health. They had three children—Carol, Eric, and Ellen—who have pursued rewarding careers. Throughout their 42 years of marriage Olive was not only a loving wife but also a friend, professional colleague, and partner in every sense of the word. Her support throughout his long illness, particularly in the last few

years, was truly monumental. It enabled Igor to do what he wanted most, to be with family and friends, and continue to pursue his love of science and research to the very end.

Igor Tamm's contributions to virology and cell biology were both enormous and varied. They began with his isolation, purification, and extensive biochemical characterization of what became known as the Tamm-Horsfall glycoprotein, named for him and his mentor. Tamm isolated the mucoprotein from human urine. He was searching for a natural inhibitor of virus replication and he chose urine as a possible source, influenced by his studies at Yale under J. P. Peters, a prominent renal expert of the day. In addition to its property as a receptor for influenza virus, the Tamm-Horsfall mucoprotein was later studied by those interested in renal function and disease. Years after Tamm's work, it was shown to have a protective effect on kidney stone formation. This mucoprotein was the first virus receptor to be isolated and purified, and thus was a landmark in virology. Many years later Tamm said he still regarded this early work as one of his most important contributions.

Because of its virus receptor activity, the mucoprotein was a competitive inhibitor of virus adsorption, the first step in virus infection, as well as a substrate for the influenza virus receptor-destroying enzyme, neuraminidase. The work with the mucoprotein was the start of a long career in the study of the inhibition of viral multiplication by both natural products and chemicals, particularly benzimidazole derivatives and guanidine.

For four decades, beginning with his paper in 1952 with Karl Folkers and Horsfall on the effect of benzimidazoles, he employed inhibitors to elucidate the biochemical and cell biological mechanisms of virus replication and its inhibition, as well as the mechanisms and prevention of virus-induced cell injury. Many viruses were involved, including influenza,

mumps, vaccinia, and adenoviruses, but the most intensively studied were the enteroviruses, particularly poliovirus. His contributions were many, highly original, and major. In these studies he enjoyed the collaboration of many students, postdoctoral fellows, and junior faculty members, including Hans J. Eggers, Lawrence A. Caligiuri, and Rostom Bablanian. With graduate student David Baltimore and Richard M. Franklin, Baltimore's primary mentor in the virology laboratory, Tamm participated in the elucidation of the synthesis of poliovirus RNA-dependent RNA polymerase. His work with the benzimidazoles as an inhibitor of virus and cellular RNA synthesis led to the use of these compounds by others in studies of cellular RNA synthesis, including James E. Darnell at Rockefeller University. Most of Tamm's work in this area was very widely recognized, however one important footnote is worthy of mention here. In a 1960 paper in the *Journal of Experimental Medicine* titled "On the Role of Ribonucleic Acid in Animal Virus Synthesis," he showed that 5,6-dichloro- β -D-ribofuranosylbenzimidazole (DRB), which he had previously found to inhibit RNA virus synthesis, inhibited adenovirus replication. However, adenovirus was a DNA virus. Tamm drew the prescient conclusion from this finding that RNA synthesis was required for DNA virus replication. Significantly, this occurred before the important description of messenger RNA (mRNA) which is copied from cellular DNA and is translated into protein. DRB was inhibiting that step in adenovirus replication.

There were many other important contributions of the Virology Laboratory at Rockefeller University under Tamm's leadership. Prominent among these was the discovery in 1963 by one of his graduate students, Peter J. Gomatos, that reovirus and wound tumor virus contained double-stranded RNA as their genetic material. This was the first description of double-stranded RNA in any biological system. Subsequently,

such RNA was found to have important roles outside of virus replication, such as in the induction of interferon and in small interfering RNAs.

Other work in different areas of virology included studies with Purnell W. Choppin, then a postdoctoral fellow, on the identification and characterization of genetic heterogeneity of influenza virus particles with respect to their interactions with cellular receptors, antibodies, and mucoprotein inhibitors of virus adsorption. These studies were done on H2N2 influenza virus strains, isolated by Choppin during the 1957 Asian influenza pandemic. One of these strains, RI/5, became one of the most widely used for studies of H2N2 influenza virus.

With graduate student Frederick Wheelock, studies were done on mitosis and cell division in cells infected with Newcastle disease virus, a paramyxovirus, and there were many other significant studies done with students, postdoctoral fellows, and collaborators, including Nicholas H. Acheson, Lawrence Alstiel, William D. Ensminger, Roger Hand, Barbara Jasny, Robert M. Krug, Frank R. Landsberger, Douglas S. Lyles, Anne G. Mosser, Suydam Osterhout, Lawrence S. Sturman, and many others.

Tamm's interest in inhibition of virus replication eventually led him to research on interferon, interleukins, and other cytokines, particularly the control of their synthesis and their effects on both normal and malignant cells. This work became his principal interest in later years. These studies were carried out over a period of almost two decades with graduate students, postdoctoral fellows, and members of the virology laboratory at Rockefeller, including Pravin B. Sehgal, Lawrence M. Pfeffer, Eugenia Wang, Toyoko Kikuchi, James S. Murphy, and James Krueger, as well as with colleagues in other laboratories at Rockefeller, such as James E. Darnell, and at other institutions, such as Jan Vilcek at New York Uni-

versity. The work included elucidation of the induction and the enhancement of interferon production by benzimidazoles and other agents, and studies of interferon mRNA synthesis and stability. Extensive work was also done on the effects of interferon on the growth, volume, division, and motility of human cells. The effects of interferon on the organization of microfilaments in cells were explored, as well as the reduction by interferon of pinocytosis by cells and of cellular insulin receptors. This work on the effects of interferon on cells helped lay the groundwork for the therapeutic use of interferon not only for viral diseases such as hepatitis but also diseases such as multiple sclerosis. His last work was focused on the role of interleukin-6 on normal and cancer cells and showed that this cytokine decreases the cell-to-cell adhesion of human ductal breast carcinoma cells. Knowledge of this kind has significance for an understanding of the metastasis of cancer cells.

In addition to those who worked directly with Tamm, there were many highly productive scientists who benefited greatly as a member of the laboratory that he headed and the excellent academic and research environment that it provided. These included Richard W. Compans, Walter H. Doerfler, Polly R. Etkind, Allan R. Goldberg, William W. Hall, Donald H. Harter, Kathryn V. Holmes, Ming-chu Hsu, Hans-Dieter Klenk, Robert A. Lamb, Sondra Lazarowitz, James J. McSharry, C. Lennart Philipson, Richard W. Peluso, Christopher Richardson, David S. Roos, Andreas S. Scheid, Samuel M. Silver, and many more.

Complementing his original research, Tamm with Frank Horsfall edited *Viral and Rickettsial Infections of Man*, which for many years was the definitive text in the field. He was an editor or member of the editorial board of several journals, including *Journal of Immunology*, *Proceedings of the*

Society for Experimental Biology and Medicine, Journal of Experimental Medicine, Biochemical Pharmacology, and Journal of Interferon Research. He served on many advisory boards and study sections for government agencies and private organizations concerned with research, including the National Institutes of Health, the Armed Forces Epidemiological Board, the American Cancer Society, and the Sloan-Kettering Institute for Cancer Research. In 1976 the National Institutes of Health turned to him to be the general chairman of the timely, comprehensive, and important Task Force on Virology.

In addition to election to the National Academy of Sciences in 1975, Tamm's honors included the Alfred Benzon Prize from Denmark (the first American to receive this award) for "outstanding research on the replication of viruses," and the Sarah L. Poiley Memorial Award from the New York Academy of Sciences.

Igor Tamm's great accomplishments in research were matched by his skills as a mentor and adviser to a very large number of young scientists who spent time in the laboratory that he headed. His students, postdoctoral fellows, and junior faculty members have gone on to highly productive research careers: professorships in universities and senior positions in research institutes around the world, working in a wide variety of departments (e.g., microbiology, virology, cell biology, genetics, biochemistry, medicine, and neurology) in the United States, Canada, Germany, France, United Kingdom, Switzerland, Japan, and other countries. Several have held responsible research positions in industry. In addition, others have gone on to senior administrative positions, such as dean or president of a large research institute or major university. Several have been elected to the National Academy of Sciences and/or received many other honors, including one Nobel Prize (David Baltimore).

On a personal note, I remember very well the first time I saw Igor. It was late in 1956 when I came to the Rockefeller Institute to discuss the possibility of my joining the lab as a postdoctoral fellow in the summer of 1957. When I met him, he was 34, tall, and rail slim; his blue eyes were sparkling, and he treated me with great courtesy. He was clearly interested in me as a person as well as a prospective fellow, and he thoughtfully took the time to show me not only around the lab but also the institute as a whole. Among those he introduced me to in the lab that day was James S. Murphy, who had joined the lab a year earlier and had the privilege of spending much of his career there with Igor until the time of his death.

I saw Igor for the last time in Watch Hill, Rhode Island, a few months before his death. He was still alert, rail slim, and his blue eyes still sparkled. I had left Rockefeller University in 1985 to join the Howard Hughes Medical Institute, but we had kept in close touch. As always he was deeply interested in what I, my wife, Joan, and our daughter were doing both professionally and personally. He was of course very enthusiastic about the work that he was still carrying out with Toyoko Kikuchi, his long-time and very talented research assistant and colleague, and James Murphy. His great spirit, courtesy, and interest in his friends and his science were undiminished by the relentless course of his disease and his dependence on the oxygen source to which he was tethered by long plastic tubes that enabled him to move around and work.

In between those two occasions there were 38 years of treasured interactions. Igor was my scientific mentor, role model, collaborator, and above all, a cherished friend. He was generous to a fault. We shared much of our scientific careers, and for 15 years he graciously allowed me to share in the leadership of the virology laboratory at Rockefeller

University, through which passed some of the most talented, intelligent, and wonderful people I have ever known. At Igor's funeral service Alexander ("Alick") G. Bearn, his close friend since 1950 and colleague at Rockefeller for many years, spoke eloquently of Igor. Near the end of his talk Alick said, "If there is one quality that captures the essence of Igor it is ..." and before he pronounced the word I knew he was going to say, "integrity," because that was so obviously the case. And it was integrity not only in his every thought and action but also in his words both spoken and written. He always spoke clearly, calmly, and precisely, in a baritone voice, each sentence meticulously crafted and grammatically correct. He was fluent in five languages, Estonian, English, German, Russian, and Swedish, and could, in his own words, "Get by in French." To know the care and precision with which Igor fashioned the written word, one had only to submit a draft of a paper to him for his comments and see, with both dismay and appreciation of its correctness, what he had done to it with his editorial pen. In the precomputer days in the lab, there were many drafts of a manuscript on yellow paper before it was ready to go on white.

Igor was a fine tennis player, and as a young scientist at Rockefeller in the late 1940s and early 1950s, he was occasionally summoned to play doubles with the indomitable director of the Rockefeller Institute Hospital, Thomas M. Rivers. Rivers was also the dean of American virology. Other young scientists there who shared in that privilege included Alick Bearn, Henry Kunkel, and Harold Ginsberg, all of whom were later elected to the National Academy of Sciences. I have been told that they wished to play on the side with Rivers as he somehow usually won. Igor's skill on the tennis court was matched by his ability as a graceful ice skater and dancer of the European School. At parties and

dances at Rockefeller when the musicians struck up a waltz, accomplished women dancers, my wife among them, would gravitate toward Igor.

Nothing is more illustrative of the great spirit and love of science, family, and friends that Igor had than his actions in the last few years of his life. After achieving professor emeritus status at Rockefeller University, and with the relentless progress of disease, shortness of breath, and dependence on oxygen, Igor and Olive moved to their home in Watch Hill, where they not only spent precious time with their family but also continued to warmly welcome friends. Through it all Igor continued his scientific work, no longer with his own hands but through daily contact by phone and mail with Toyoko Kikuchi and James Murphy. Always uncomplaining and eager to discuss his research with colleagues, his work flourished. In the last year of his life he published three major papers and others were in preparation. On the last day of his life Igor was making notes for his next conversation with Toyoko about the work in the lab. He died peacefully in his sleep.

No one fits better than Igor Tamm the words of Shakespeare in *Henry VIII*: “He was a scholar and a ripe and good one; exceeding wise, fair-spoken, and persuading.”

A great many of us had the privilege to know Igor as a student, fellow, or colleague, and a true friend. Whether with him for only a few or for many years, we remember this gentle, wise, extraordinarily capable, loyal man with great respect and affection. We all owe him very much.

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