7-1-2019

Ion Gresser 1928-2019

Jan Vilcek
NYU Langone Health

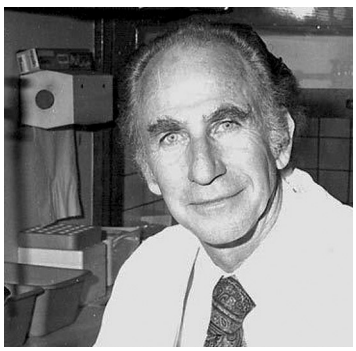
Howard A. Young
National Cancer Institute at Frederick, younghow@mail.nih.gov

Ion Gresser 1928–2019

Ion Gresser, a virologist who transformed understanding of the roles of interferons, may be best remembered for showing that in mice, interferon-α (IFN-α) can produce acute and chronic disease. At the time Gresser began these studies, interferon was considered to be a selective antiviral substance, harmless to uninfected cells and organisms, and there was no indication that cytokines would play a role in pathogenesis. That belief was shattered with the 1975 *Nature* publication with the simple title "Lethality of interferon preparations for newborn mice."

Gresser subsequently demonstrated that antibodies to IFN-α can protect young mice from death caused by infection with lymphocytic choriomeningitis virus. This study can be considered a stepping-stone for the therapeutic application of antibodies to cytokines in the treatment of human disease, which was introduced much later and revolutionized the management of some autoimmune diseases.

Since its first description by Alick Isaacs and Jean Lindenmann in 1957, interferon was believed to be important in an organism's resistance to viral infection and was thought to have the potential to become as useful in the treatment of viral diseases as penicillin and other antibiotics had turned out to be for infections caused by bacteria. Gresser made substantial contributions to the body of knowledge about interferon that is now taken for granted. His early studies of mouse models of viral infections established that injections of IFN-α can indeed protect mice from viral infection. Gresser was among the first investigators to explore the potential of interferons in the control of malignancies in animal models, showing that it can protect mice not only from leukemias caused by viruses but also from solid tumors and metastatic cancer. Those findings contributed to the original optimism about the potential usefulness of interferons not only in the treatment of viral infections but also in the control of cancer in humans. Unfortunately, those expectations were generally not borne out by later clinical trials. Although interferon therapies would show moderate efficacy in the control of some viral infections, such as chronic active infection with hepatitis virus B or C, and even more modest results in some malignancies, the benefits fell short of the initial expectations.



More surprising at the time was the first demonstration, by Gresser and colleagues in 1973, that IFN-α enhances the expression of histocompatibility antigens and modifies the surface of uninfected cells, and that it has other immunomodulatory actions. Those last findings were among the first demonstrations that interferons have actions separate from their antiviral activities and broadened the scope of interferon research.

A native of New York City, Gresser developed early on an appreciation of science and the arts. His mother, Gisela Kahn Gresser, was a classicist and prominent chess player who dominated women's chess for more than three decades, winning nine national titles between 1944 and 1969. His father, William Gresser, a successful attorney, moonlighted as a serious musicologist. Ion Gresser — who too retained a life-long passion for the piano and classical music — completed his undergraduate studies at Harvard University. In addition to science, he was interested in history, European literature and Russian.

After his graduation from Yale School of Medicine and an internship at Bellevue Hospital in New York City, he joined the army and served as head of an infectious disease laboratory at the army post in Camp Zama, Japan. There he developed an active interest in virology and published his first papers on Japanese encephalitis and Asian flu — a passion that blossomed during a postdoctoral fellowship in the laboratory of John F. Enders, the Harvard-based virologist and co-recipient of the 1954 Nobel Prize in physiology or medicine. While working in Enders' lab, Gresser also published his first paper devoted to interferons.

A Francophile, Gresser moved to Paris in the early 1960s, first joining the laboratory of another interferon pathfinder, Charles Chany, at the Hôpital St. Vincent de Paul, and soon thereafter establishing his own laboratory at the Institut de Recherches Scientifiques sur le Cancer in Villejuif, outside Paris. Eventually, Gresser ended up spending decades at the Villejuif laboratory, and it was there that he conducted all of his many original studies for which he became known. Although he retired from his position at Villejuif many years ago, he continued to publish reviews, as well as original research in collaboration with others. His very last paper, co-authored with Pierre Lebon, Yanick Crow and Jean-Laurent Casanova, appeared in March of this year, only weeks before his passing.

Arguably, the most important contribution of Gresser and his colleagues was the demonstration of harmful effects of interferons in animal models, as well as the clear evidence that interferons contribute to pathogenesis, including the pathogenesis of viral infections. Among the most surprising discoveries was that injection of mice with potent sheep immunoglobulin directed against IFN-α markedly inhibits the manifestations of disease caused by infection with lymphocytic choriomeningitis virus (weight loss, liver-cell necrosis and death), despite the fact that the treated mice had 100-fold more of the virus in their serum than did mice that were not treated with the anti-interferon immunoglobulin. At the time of their publication in 1977, these findings not only were completely unexpected and counterintuitive but also presaged the advent of the dramatic beneficial effects of anti-cytokine therapies in humans, such as those achieved with the use of monoclonal antibodies to the cytokine TNF in the treatment rheumatoid arthritis, Crohn's disease and some other autoimmune disorders. This discovery alone would be sufficient to earn Ion Gresser a lasting abode in the pantheon of medical science. ❐

Jan Vilcek[1*] and Howard A. Young[2]
[1]*Department of Microbiology, NYU Langone Health, New York, NY, USA.* [2]*Center for Cancer Research, National Cancer Institute, Frederick, MD, USA.*
**e-mail: jan.vilcek@nyumc.org*

Published online: 10 June 2019
https://doi.org/10.1038/s41590-019-0428-8