In Memoriam: Jean Lindenmann (1924-2015)
A Circuitous Interfering Power in Neurology

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Sometimes, the intended consequences of scientific discovery are not the ones that ultimately have the greatest impact on humanity. This is certainly the case of the interferons, which were discovered jointly by Jean Lindenmann and Alick Isaacs in an attempt to elucidate the role of interferons in host innate immune responses against viral infections.

Dr Lindenmann, a Swiss virologist who passed away on January 15, 2015, in Zürich, Switzerland, was an outstanding scientist whose contributions to the interferon field were groundbreaking. He joined Dr Isaacs in the mid-1950s as a postdoctoral fellow at the National Institute for Medical Research in Mill Hill in London, England. The purpose of his research was to study the nature of “viral interference.” When he commenced his work it was already established that incubation of a tissue or tissue culture with heat-inactivated virus could prevent the replication of a virus that was subsequently added. Drs Lindenmann and Isaacs subsequently demonstrated that fluid conditioned for 24 hours with chick chorio-allantoic membranes exposed to inactivated virus could transfer this “interfering power” to fresh membranes, indicating that additional “interfering activity” had been generated. Dr Lindenmann then showed that a certain time lapse was required to obtain interference, suggesting that a new protein had to be generated to achieve this. Furthermore, dilution experiments indicated a linear relationship between the concentration of interferon and its antiviral potency. The seminal article reporting the discovery of interferons was published in 1957, which ultimately proved to be a family of proteins with a very high specific activity and a broad spectrum of biological effects.

Dr Lindenmann returned to Zürich but did not pursue the purification and structural analysis of interferon. He was convinced that this task would be more or less rapidly accomplished by biochemists. In retrospect, this decision may appear misguided: Thousands of man-years later, in 1980, Ernest Knight remarked that “the best way to describe the progress in purification and characterization of the interferon proteins is that it has just begun.” At that time, the multiplicity of interferon species and the low levels of production proved to be an almost unsurmountable barrier. Rather than purifying interferon, Dr Lindenmann explored its mechanism of action and identified a dominant autosomal gene, which he called Mx (now called Mx’), that mediated interferon-induced resistance against influenza and some other viruses. The Mx promoter is a powerful tool to direct controlled expression of a downstream gene and is now widely used in inducible gene expression in experimental mice.

After 1980, research in the interferon field progressed rapidly as recombinant DNA technology clarified the relationship between the many interferon species and allowed the production of pure interferon on the kilogram scale. Most importantly, the generation of interferons on an industrial scale led to legitimate clinical applications. In 1987, Hillel Panitch, MD, and colleagues conducted a clinical trial with interferon gamma in patients with relapsing-remitting multiple sclerosis (MS). At that time, many MS experts considered MS to be a viral, postviral, or paraviral disorder, which made interferon gamma a plausible intervention. Unexpectedly, a disproportionate number of patients displayed disease exacerbations, and bioassays detected an increase in circulating HLA-DR-positive monocytes in peripheral blood of recipients. These observations strongly suggested that MS disease exacerbations are immune mediated and not the consequence of viral illness.

In contrast, interferon beta preparations have been approved and used for the treatment of MS for more than 20 years. The biological beneficial effects of interferon beta in MS, which include the reduction of disease attacks and brain lesions on magnetic resonance imaging, are pleiotropic and still incompletely understood. The recent approval of pegylated interferon beta-1a will likely ensure that they remain a mainstay of MS therapy for decades to come. Thus, Dr Lindenmann’s discovery not only opened up a new area of basic research, but also led to practical medical benefits.

Those who knew Dr Lindenmann describe him as a gifted communicator who time and again delighted laymen and colleagues alike with his philosophical and historical discourses on scientific topics. Modest and unassuming, he kept out of the limelight toward which many another with his accomplishments would have striven.
Obituary


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Conflict of Interest Disclosures: Dr Stüve serves on the editorial boards of JAMA Neurology, Multiple Sclerosis Journal, and Therapeutic Advances in Neurological Disorders. He has received grant support from Teva Pharmaceuticals and Opexa Therapeutics. Dr Stüve has served on data monitoring committees for Pfizer and Sanofi without monetary compensation. He has served on an advisory board for Genzyme. Dr Stüve is funded by a Merit grant from the US Department of Veterans Affairs.