Foreword

Celebrating the 50th Anniversary of the Discovery of Interferon

IN 2007 interferon researchers throughout the world will celebrate the 50th anniversary of the discovery of interferon by Isaacs and Lindenmann.¹ That seminal finding launched a new era in our understanding of viral interference, and what was to become a new class of potent biological response modifiers—cytokines. In recognition of that momentous event, the *Journal of Interferon & Cytokine Research* will publish a series of articles, starting with contributions from pioneers in interferon research, who will recount their early experiences in a fledgling field at a time where virtually every experimental result provided new insights into viral interference mediated by the interferon system. Collectively, these Historical Perspective articles will provide an archive of the interferon field beginning with accounts from the individuals who contributed the signature research in the precloning era that served as the fountainhead and foundation on which the field rests. The Archive Committee of the International Society for Interferon and Cytokine Research deserves accolades for its efforts to preserve for the future what most certainly will be counted as a major discovery and the first glimpse into the ever-expanding world of cytokines.²

In 2004 there was a comparable celebration by our Japanese colleagues for the 50th anniversary of the discovery of *facteur inhibiteur/virus inhibitory factor* by Nagano and Kojima.³ This event represented a continuing effort to gain appropriate recognition for two other pioneers in viral interference research. Indeed, as the history surrounding the discovery of virus inhibitory factor unfolds against that of interferon, it reveals a phenomenon not exactly foreign to science, namely, the independent development of a common discovery. In the case of interferon/virus inhibitory factor, these two discoveries, though separated by three years, appear to qualify as independent events. However, the events surrounding the delay in recognition of virus inhibitory factor as part of the history of interferon are more complex than a simple recounting of the dates of their initial publication. These issues are addressed and elegantly recounted in an upcoming article by Keiko Ozato, Kazuko Uno, and Yoichiro Iwakura, which provides a thorough and fascinating account of the discovery of virus inhibitory factor by Nagano and Kojima, and the complexities surrounding its acceptance as interferon.

These early studies on viral interference and the factors involved did not escape the keen observations of William E. Stewart II. In Stewart's 1982 classic text, *The Interferon System*,⁴ he noted several early workers who, unbeknownst to them, most likely were working with interferon. In particular he refers to

the studies of Nagano and Kojima and astutely comments; "... indeed, 'facteur inhibiteur' seems to qualify as an interferon (or should it be the other way around?)." By 1959, the then-virus inhibitory fluid/factor of Ho and Enders was described in yet a third virus-cell system,⁵ and then graciously acknowledged to be interferon,⁶ as was the case in the perceptive studies of persistent infection and viral interference described by the Henles.⁷

Yet, equating virus inhibitory factor with interferon was slow in coming. In 1987, a Commemorative Issue of the *Journal of Interferon Research* was published to celebrate the 30th anniversary of the discovery of interferon and pay tribute to Jean Lindenmann.⁸ The 35 contributors to this special issue provided early, and personal, accounts of their experience with the interferon system, or in some cases, their close encounters with its discovery. Monto Ho commented that Nagano was probably working with interferon. Clearly, many researchers flirted with the discovery of IFN,⁸ but Bob Friedman should be credited with identifying what was possibly the first recorded example of an interferon-mediated effect. Measles infection in a boy delayed the appearance of the typical cow-pox "efflorescence" following vaccination—as described by Edward Jenner in 1799 (see p. 452 in ref. 8). Collectively, these 1987 writings chronicle many fascinating developments in interferon research as its molecular nature and modes of action began to unfold.⁸ The Historical Perspective articles slated to appear in the *Journal of Interferon & Cytokine Research* in 2007 represent a continuum of the recorded history of the field.

We are fortunate and privileged to have the first article in this 50th anniversary year contributed by Jean Lindenmann.⁹ His personal account of working with Alick Isaacs takes the reader back some 50 years to capture the state of knowledge on viral interference at the time, as he shares the thinking and events that led to the discovery of the heretofore elusive, and the aptly named molecule—interferon. In the second article, Derek C. Burke paints a vivid picture of his work with Isaacs. It places the reader in the laboratory producing fragments of chorioallantoic membranes to make and measure the chicken interferon produced by them in response to heated-, or better still, UV-inactivated, influenza virus. Some of those experiments were repeated almost five decades later, again in chicken cells, confirming the original results in their entirety.¹⁰ The flavor of conducting research with Isaacs will continue in forthcoming articles by Robert M. Friedman and Samuel Baron.

Some investigators initially active in interferon research, or now retired, graciously declined to contribute an account of

their early research. One such individual justified declination by noting a previous 239-page publication on the subject—a point difficult to countermand. Nevertheless, Kari Cantell's *The Story of Interferon: The Ups and Downs in the Life of a Scientist*,¹¹ and Norman Finter's thorough review,¹² add to the historical account of the discovery and use of interferon. There were other people in this category who, in the 1970s championed the development of interferon as a natural product with potential clinical use as an antitumor or antiviral agent. Notable among them were Mathilda Krim, whose Herculean efforts to gain federal support for interferon research were eminently successful, and clinicians who put it to the test: Hans Strander, Thomas Merigan, and Jordan Gutterman.

Sadly, some pioneers of interferon research are no longer with us. Most notable are Alick Isaacs (1921–1967), and Yasuichi Nagano (1906–1998).¹³ Their accounts would have been invaluable, as would those of William E. Stewart II (1940–2000),¹⁴ a major contributor to the recognition of interferon and its advancement as a valid research entity. He, no doubt, would have provided a lively article. His prolific writing and classical textbook,⁴ coupled with being founder of the progenitor to the *Journal of Interferon & Cytokine Research*, and the International Society of Interferon and Cytokine Research, made him a formidable, albeit controversial figure, in interferon research. Indeed, contributors to his obituary, which includes a self-portrait as an example of his artistic talent, revealed the multifaceted complex personality that was Bill Stewart.¹⁴ His place in the annals of interferon research is nonetheless assured.

Edward De Maeyer (1932–2003) and Jaqueline De Maeyer-Guignard (–2006) were interferon researchers extraordinaire. A memorandum to Ed De Maeyer by 11 of his colleagues makes it abundantly clear that he was a towering figure in the field.¹⁵ While always magnanimous and always the gentleman, Ed did rise to the occasion when a colleague cast doubt on the priority assigned to a study that was clearly the first to describe the detection of interferon by translation of its mRNA in heterologous cells.¹⁶ This discovery was but one of many firsts for Ed and Jaqueline. Their research benefited greatly from their lifetime of collaboration and the natural synergy that was evident between husband and wife. Their coauthored text stands as a lasting example of their command of, and contributions to, the interferon field.¹⁷

Since its inception in 1980–1981, the *Journal of Interferon* and its successor, the *Journal of Interferon & Cytokine Research*, have chronicled the passing of several interferon researchers of note. They are listed here with citations to their obituary where their contributions are often described: Kurt Paucker (1924–1980);¹⁸ Piet De Somer (–1985);¹⁹ Shigeyasu Kobayashi (1935–1993);²⁰ Giovanni B. Rossi (1937–1994);²¹ István Rosztóczy (1943–1993);²² Christina M. Fleischmann (1945–1996);²³ Yukio Mitsui (1938–2000).²⁴ A debt of gratitude is extended to those colleagues who have not been so recognized but whose contributions have been spread richly upon the literature.

The contributors of articles that will appear in the 50th anniversary issues of the *Journal* were chosen by the chief and consulting editors of the *JICR* after input from many respected researchers in the field. They represent pioneers in interferon research, most of whom have devoted their careers to the study

of interferon and advanced it by contributing significantly to the field. While the interferon field has mourned the loss of several of its founders who could have enriched the archives of our discipline, perhaps the greatest loss was that of Alick Isaacs who, at a young age, did not live to see even a small fraction of the advances in interferon and other cytokine research for which his seminal studies laid the foundation. This is a subtle reminder to those of you who have been invited to submit contributions—sooner is better than later!

Lastly, I note that for the 50, and 53, years since the discovery of interferon and virus inhibitory factor, respectively, Mary Ann Liebert, the publisher of the *Journal of Interferon & Cytokine Research*, and its progenitor, the *Journal of Interferon Research*, has provided strong and continued support for the dissemination of interferon and other cytokine research for 27 of those years. She and the staff at Mary Ann Liebert, Inc., have earned our heartfelt gratitude. Sidney Milstein, and now his family, also deserve recognition for their long-term support of interferon research in the form of the Milstein Award. The recipients of this award have graced the pages of this journal for almost two decades with articles describing their exemplary research. Both Mary Ann Liebert and Sidney Milstein have earned a place in the archives of interferon research as well.

REFERENCES

1. Isaacs A, Lindenmann J. Viral interference. I. The interferon. *Proc. Royal Soc. Series B*. 1957;147:258–267.
2. Finter NB. The archive of the International Society for Interferon and Cytokine Research. *J. Interferon Cytokine Res* 1999;19:693–694.
3. Nagano Y, Kojima Y. Pourvoir immunisant du virus vaccinal inactive par des rayons ultraviolets. *Comptes rendus des séances de la Société de Biologie*. 1954;148:1700–1702.
4. Stewart WE II. In: *The Interferon System*, 2nd ed. Vienna & New York: Springer-Verlag, 1981, 493 pages.
5. Ho M, Enders JF. Inhibitor of viral activity appearing in infected cell cultures. *Proc. Natl. Acad. Sci. USA*. 1959;45:385–389.
6. Ho M. An early interferon: “Viral inhibitory factor.” *J. Interferon Res*. 1987;7:455–458.
7. Henle W, Henle G, Deinhardt F, Bergs VV. Studies on persistent infections of tissue cultures. IV. Evidence for the production of an interferon in MCN cells by myxoviruses. *J. Exp. Med*. 1959;110:525–541.
8. Marcus PI. (Ed.). Commemorative issue. A tribute to Jean Lindenmann, celebrating the 30th anniversary of the discovery of interferon. *J. Interferon Cytokine Res*. 1987;7: v429–671.
9. Lindenmann J. Interferon and before. *J. Interferon Cytokine Res*. 2007;27(1):2–5.
10. Marcus PI, Rojek JM, Sekellick MJ. Interferon induction and/or production and its suppression by influenza A viruses. *J. Virol*. 2005;79:2880–1890.
11. Cantell K. *The Story of Interferon: The Ups and Downs in the Life of a Scientist*. Singapore: World Scientific Publishing Co., 1998; 239 pages.
12. Finter NB. Review of *The Story of Interferon: The Ups and Downs in the Life of a Scientist*, by K. Cantell. *J. Interferon Cytokine Res*. 2000;20:345–346.
13. Imanishi J. Obituary: Yasuichi Nagano (1906–1998). *J. Interferon Cytokine Res*. 2000;20:925.
14. Marcus PI, Liebert MA, Friedman RM, Tovey MG, Havell EA, Sonnenfeld G, De Maeyer E, Gresser I. Obituary: William E. Stewart II. *J. Interferon Cytokine Res*. 2000;20:839–841.

15. Marcus PI, Gresser I, Vilcek J, Pitha-Rowe P, Baron S, Friedman RM, Tovey MG, Montagnier L, Sonnenfeld G, Fleischmann WR, Epstein LB. In memoriam: Edward De Maeyer (1932–2003). *J. Interferon Cytokine Res.* 2003;23:683–688.
 16. De Maeyer-Guignard J, De Maeyer E, Montagnier L. Interferon messenger RNA: Translation into heterologous cells. *Proc. Natl. Acad. Sci. USA.* 1972;69:1203–1207.
 17. De Maeyer E, De Maeyer-Guignard J. *Interferons and Other Regulatory Cytokines*. New York: John Wiley & Sons, 1988:449 pages.
 18. Stewart WE, II. Dedication: Kurt Paucker. *J. Interferon Cytokine Res.* 1980/1981;1:v.
 19. Billiau A. Obituary: Piet De Somer. *J. Interferon Cytokine Res.* 1985;5:529–530.
 20. Azuma M. Obituary: Shigeyasu Kobayashi. *J. Interferon Cytokine Res.* 1993;13:311.
 21. Dianzani F, Baron S, Pestka S. Obituary: Giovanni B. Rossi. *J. Interferon Cytokine Res.* 1994;14:99.
 22. Béládi I. Obituary: István Rosztóczy. *J. Interferon Cytokine Res.* 1994;14:145.
 23. Fleischmann WR. Obituary: Christina M. Fleischmann. *J. Interferon Cytokine Res.* 1997;17:179.
 24. Senda T, Utsumi J, Naruse N. Obituary: Yukio Mitsui. *J. Interferon Cytokine Res.* 2000;20:533–537 (English and Japanese).
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