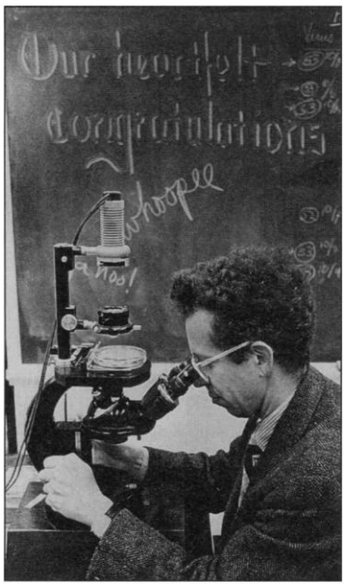
BOOK REVIEWS

Foresighted Virology

The DNA Provirus. Howard Temin's Scientific Legacy. GEOFFREY M. COOPER, RAYLA GREENBERG TEMIN, and BILL SUGDEN, Eds. ASM Press, Washington, DC, 1995. xxxii, 324 pp., illus. $75. From a symposium, Madison, WI, Oct. 1994.

Howard Temin was a key figure in the development of tumor virology and cancer biology. He died at the age of 59 on 9 February 1994. In December of that year a commemorative symposium was held in Madison, Wisconsin, where Temin had worked since 1960 as a member of the McArdle Laboratory for Cancer Research. The symposium was attended by former trainees and associates from the McArdle Laboratory and by colleagues in the field who had been influenced by Temin's work. This volume includes some of the papers presented at the symposium: they describe current research in animal virology and the molecular biology of cancer and trace the origin of these developments to Temin's early observations. It also includes a biographical portrait by his wife, Rayla Greenberg Temin, and reprintings of selected papers by Temin or his group, each with a brief introduction. Together these essays and papers provide a view of the development of modern virology and cancer biology and Howard Temin's contributions to these fields; they also provide a view of a scientist who inspired much respect and affection.



"Howard Temin in his laboratory on the day the Nobel Prize was announced, 16 October 1975." [From *DNA Provirus*]

Temin's career began at Caltech in the late 1950s. As a graduate student he worked with Harry Rubin, then a postdoctoral fellow in Renato Dulbecco's group, to develop the focus assay for Rous sarcoma virus. This led in 1960 to the identification of morphological variants of Rous sarcoma virus and to the idea that viral genetic information was involved in transformation, an idea that was confirmed a decade later by the isolation of temperature-sensitive and deletion mutants. Temin will of course be best remembered for his formulation of the provirus hypothesis and for the defense of the hypothesis against spirited attack. The idea that RNA could direct the synthesis of DNA seemed to be heretical and to run counter to the central dogma of molecular biology. Yet, as Francis Crick pointed out at the time, the central dogma precludes the flow of information from protein to nucleic acid, not from RNA to DNA. The papers reprinted in this volume review the experiments that led to the idea of the provirus, the experiments with inhibitors that provided circumstantial support for it, and the discovery of reverse transcriptase, which in 1970 finally silenced the critics.

The discovery of retroviral reverse transcriptase and the confirmation of the provirus hypothesis led Temin a year later to propose that retroviruses had evolved from genetic elements that duplicated by reverse transcription and that reverse transcription was involved both in normal development and in carcinogenesis. The first part of this model, the protovirus hypothesis as he called it, had received some support by the end of the 1970s, when it was shown by a number of groups that the proviral long terminal repeats and host-provirus junctions resembled analogous structures of certain cellular transposons; one of Temin's papers describing these findings is included in the present volume. However, it was only in the mid-1980s, with the biochemical characterization of virus-like particles encoded by the *Drosophila* transposon *copia* and the genetic demonstration that the yeast element Ty1 transposes via an RNA intermediate, that the existence of cellular retrotransposons became generally accepted. The second prediction of the protovirus hypothesis, that retrotransposition plays a role in cellular differentiation and oncogenesis, appears to apply only in a few limited instances. Nevertheless, as Geoffrey Cooper and Michael Bishop stress, Temin's ideas provided an alternative to the oncogene hypothesis of Huebner and Todaro, who had proposed in 1969 that cancer was due to the activation of vertically transmitted proviruses; the protovirus hypothesis, with its focus on somatic genetic alterations and recombination between provirus and cell, thus presaged the discovery of proto-oncogenes by Varmus and Bishop. In later years Temin continued to be interested in carcinogenesis, but his work on viral transformation was centered not on his earlier love, Rous sarcoma virus, but on the then relatively obscure avian reticuloendotheliosis viruses. Tom Gilmore describes the identification of the transforming protein of this virus and the discovery that it is derived from a member of a conserved family of transcription factors that regulate immune and inflammatory responses.

Temin's primary interest, however, continued to be the mechanism of retrovirus replication. His group worked on the structure, synthesis, and integration of viral DNA, the transmission and evolution of endogenous proviruses, the mechanism of retroviral recombination, and the role of error-prone reverse transcription in generating retroviral mutants. Retroviral variation, which Temin believed to result from errors in strand transfer during reverse transcription, has proven to be of central importance in understanding the pathogenic progression of AIDS; in a lucid and stimulating review, John Coffin discusses both the evolution of endogenous viruses and the dynamics of HIV infection. Temin was very active in promoting research on AIDS, and the final paper in this volume is his proposal for an HIV vaccine based on a simplified but replication-competent variant of HIV-1.

Two groups of readers will be interested in browsing through the papers and essays in this book. Some will be interested in the scientific history of the field and in tracing the origins of molecular oncology and AIDS research from their roots in the study of avian retroviruses. A second, perhaps smaller group will include colleagues who would like to be reminded of a modest but very determined individual who was a deep thinker, a proponent of "backwater science," and a dedicated mentor: in the editors' words, a "scientist's scientist."

G. Steven Martin
Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720–3204, USA