
Howard M. Temin

(1934 – 1994)

- **Formulator of the Provirus Hypothesis for Retrovirus Replication**
- **Discoverer of Reverse Transcriptase**
- **Nobel Laureate**
- **Dedicated Teacher and Mentor**



From 1960 until his untimely death from cancer in 1994, the University of Wisconsin - Madison and its McArdle Laboratory for Cancer Research were the professional home of Professor Howard M. Temin, a Nobel Prize-winning virologist who made revolutionary contributions to basic biology and medicine while continuing as a dedicated classroom teacher.

Howard Temin's achievements exemplify the value of a resolutely analytical approach to research and the determined use of insightful experimentation to follow a line of results despite the unorthodoxy and unpopularity of the conclusions that emerged, and provide a striking example of how the focused work of one scientist can change how we all think.

Temin's Early Work in Retrovirology

Howard Temin began to investigate viruses as a young graduate student at the California Institute of Technology in the late 1950's with Dr. Renato Dulbecco. The animal viruses most studied at the time were influenza virus and poliovirus, but Howard chose to work on the cancer-causing Rous Sarcoma Virus (RSV). One of his early contributions was to develop a quantitative focus assay that remains a

standard tool for genetic studies of transforming viruses in cell culture.

Formulation – and General Rejection – of the “Provirus” Hypothesis

Temin moved to the McArdle Laboratory in the University of Wisconsin Medical School in 1960, where he continued to characterize the life cycle of RSV in cultured cells. He and some others found that, although RSV virions contained RNA, inhibition of DNA

synthesis or DNA-dependent RNA synthesis inhibited production of RSV from infected cells.

These observations led Temin to propose that RSV maintained itself in infected cells as a DNA "provirus" from which the encapsidated RSV RNA was synthesized. This heretical view was met with general disdain. In fact, when Temin first proposed this hypothesis in a paper, the referees and editors required that he remove the suggestion that the

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proposed RSV "provirus" might represent a DNA form of the viral RNA.

Despite such discouragement from others in the field, Temin continued to explore the implications of his results. In further studies, Temin found that the outcomes of varied genetic and biochemical experiments continued to support the provirus hypothesis. However, these results still failed to win acceptance in the field.

The Demonstration of Reverse Transcriptase

By 1969, through testing the effects of protein synthesis inhibitors on the establishment of RSV infection, Temin realized that the proviral DNA must be synthesized by a reverse transcriptase brought into infected cells within the RSV virion. Working with Satoshi Mizutani, a postdoctoral fellow, he developed biochemical assays that unequivocally demonstrated the presence of RNA-dependent DNA polymerase in RSV virions. David Baltimore, who had known Temin since high school and had followed his provirus hypothesis with interest, conducted similar tests of murine leukemia virus, finding an equivalent activity there. Their landmark papers were published together in *Nature* on June 27, 1970.

The biochemical demonstration of reverse transcriptase won almost immediate acceptance for the previously unpopular provirus hypothesis. Moreover, the general importance of this result, overturning the then "central dogma" of unidirectional information flow from DNA, was immediately perceived throughout molecular biology. Thus, in 1975, Temin was awarded the Nobel Prize in medicine for a line of research that had previously been shunned.

Temin's Further Retrovirus Research

In the following years, Temin and his students and postdoctoral

fellows pursued many basic problems in retroviral replication and genetic variation. Among other results, they demonstrated that retroviruses use splicing to generate certain mRNAs, but must keep some of their transcripts unspliced to maintain their genetic information intact. They identified the retroviral *int* gene required for integration of the proviral DNA and the nucleotide changes imposed on the provirus as a consequence of its mechanisms of synthesis and integration. They developed helper cells that provide all trans-acting retroviral functions, and thus support the replication and packaging of retroviral vectors containing only the cis-acting viral elements. Using these helper cells, they developed procedures to measure the types and frequencies of mutations that occur in a single round of retroviral replication. Their studies revealed the high frequency and wide variety of retroviral mutation and recombination events and explored the mechanisms that generated these changes, enhancing understanding of normal retrovirus replication.

Teaching and Service

Throughout his extraordinarily productive scientific career, Temin also contributed in other important arenas beyond his own research. Though it was not widely known beyond the Madison campus, he was a dedicated classroom teacher and, with William McClain, taught a general virology course for nearly 30 years. Temin applied considerable effort to his lectures, employed novel visual aids and models to illustrate important principles, and each year pored over the students' reviews of the course to find ways to improve the lectures. His commitment to teaching came from a keen sense of the importance of training the next generation of scientists, colleagues and citizens.

Temin was also an outspoken advocate on a number of public health issues, notably smoking,

against which he spoke ardently on many public occasions, including his Nobel prize acceptance speech. Before the Human Immunodeficiency Virus (HIV) received its name, he recognized that AIDS would reach epidemic proportions and worked to increase U.S. funding for AIDS research. He chaired the subcommittee on AIDS of the National Cancer Advisory Board and served on the World Health Organization Advisory Council on HIV and AIDS. When he received the National Medal of Science at the White House in 1992, he used the occasion to appeal to the President for increased funding of biomedical research.

Howard Temin's Last Struggle against Cancer

Two months after receiving the National Medal of Science, Temin was diagnosed with adenocarcinoma of the lung, a tumor type unrelated to smoking, which he had never practiced. With characteristic strength and humor, soon after his diagnosis he told the Dean of the UW-Madison Medical School that he now knew a way to interest basic researchers in clinical medicine, although it had some drawbacks. He fought his illness with amazing spirit and determination. He apprised himself of the current therapies for his tumor and went on to accept two new experimental therapies.

Despite the physical afflictions of his cancer and its aggressive treatment, Howard Temin continued to supervise his laboratory and worked tirelessly throughout his illness for the sake of his students and postdoctoral fellows. 15 of his over 300 publications were completed after he was diagnosed with cancer. The final thesis exam of his last Ph.D. student was held, with his attendance, almost exactly one month before his death, which occurred on February 9, 1994. A devoted family man, he is survived by his wife, Rayla Greenberg Temin, and two daughters.