

# This Week's Citation Classic®

Temin H M & Baltimore D. RNA-directed DNA synthesis and RNA tumor viruses.

*Advan. Virus Res.* 17:129-86, 1972.

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This paper was one of the first reviews published about what is now called reverse transcriptase. It gave a comprehensive review of the enzyme and its biological role in retrovirus replication. [The SCJ® indicates that this paper has been cited in over 370 publications, making it this journal's most-cited paper.]

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The discovery in 1970 of reverse transcriptase in Moloney murine leukemia virus by David Baltimore<sup>1</sup> and in Rous sarcoma virus by Satoshi Mizutani and me<sup>2</sup> established the validity of the DNA provirus hypothesis, which states that RNA tumor viruses replicate through a DNA intermediate. It started a flood of research that has still not crested.<sup>3,4</sup> Shortly after this discovery, the editor of *Advances in Virus Research* asked Baltimore and me to write this review, which has become a *Citation Classic*. Baltimore wrote the first draft of the more biochemical sections, and I wrote the first draft of the more biological sections. We exchanged drafts, made corrections, and finished the review at the end of 1971. As I remember, the only real problem we had with this joint enterprise was what to do with the flood of new information that appeared after the review was written but before it was printed. The problem was resolved with the publication of two sets of references, added in proof.

Although the study of retroviruses and reverse transcriptase has moved rapidly, much

of the basic information in this first review is still valid, and the review still seems to be accepted as authoritative. Thus, in spite of many more recent reviews, it still is referenced. In fact, after no references in 1986, there were eight in 1987 and eight more in the first half of 1988. About half of these references were in articles about human immunodeficiency virus, but others were about retroviruses, oncogenes, hepatitis B virus, and DNA polymerases in general.

Reverse transcriptase was first discovered in what were then called RNA tumor viruses and was first called RNA-dependent DNA polymerase or RNA-directed DNA polymerase. It was then discovered in some other RNA viruses. All of these RNA viruses are now called retroviruses, although this term was not yet established at the time the *Citation Classic* was written. "Leukovirus" and "rousvirus" are other now-forgotten names used in the review. Subsequently, reverse transcriptase was looked for in uninfected cells, but the results from these experiments are still unclear. Now DNA sequences homologous to reverse transcriptase and even reverse transcriptase activity itself have been found in, or associated with, many cellular movable genetic elements and hepadnaviruses and caulimoviruses. In addition, many cDNA or processed genes in the cell genome appear to represent the products of reverse transcription, although the nature of the reverse transcriptase activity responsible for their formation is still unknown. Some have even speculated that certain properties of reverse transcription may be remnants of the transition from life based on RNA to life based on DNA.<sup>5</sup> Thus, there is, if anything, more interest in reverse transcriptase now than when it was first discovered and this review was written.

Baltimore and I have recently collaborated, with others, in writing the Institute of Medicine/National Academy of Sciences reports *Confronting AIDS* and *Confronting AIDS: Update 1988*.<sup>6,7</sup>

1. Baltimore D. Viral RNA-dependent DNA polymerase. *Nature* 226:1209-11, 1970. (Cited 1,125 times.)
2. Temin H M & Mizutani S. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. *Nature* 226:1211-3, 1970. (Cited 1,165 times.) [See also: Temin H M. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life*. Philadelphia: ISI Press, 1986. p. 159.]
3. Weiss R, Teich N, Varmus H & Coffin J, eds. *RNA tumor viruses*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1982. 1,396 p.
4. ———, eds. *RNA tumor viruses. Supplements and appendixes*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1985. 1,233 p.
5. Weiner A M & Maizels N. tRNA-like structures tag the 3' ends of genomic RNA molecules for replication: implications for the origin of protein synthesis. *Proc. Nat. Acad. Sci. USA* 84:7383-7, 1987.
6. Committee on a National Strategy for AIDS, Institute of Medicine. *Confronting AIDS: directions for public health, health care, and research*. Washington, DC: National Academy Press, 1986. 35 p.
7. Committee for the Oversight of AIDS Activities, Institute of Medicine. *Confronting AIDS: update 1988*. Washington, DC: National Academy Press, 1988. 239 p.