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July 27, 1976

Dr. Edward Fritsch and
Dr. Howard Temin
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University of Wisconsin
Madison, Wisconsin 53706

Dear Ed and Howard:

Many thanks for sending your preprint; the work is interesting and impressive. I am particularly intrigued by the absence of infectious DNA in the infected stationary cultures; I got a report from Cold Spring Harbor that chemically-detectably viral DNA is present in such cells. Is this so? Do you know anything about the structure of such DNA? We have some fairly good evidence that S phase is required for integration of ASV DNA: (If cells are infected in the presence of BUdR, viral DNA (heavy-heavy) integrates into heavy-light cell DNA but not into light-light DNA.) Our results and yours may mean that some product made in phase is required to convert viral DNA into a form which is "integratable" and infectious.

As you probably heard from Pete Shank, we also find the principal cytoplasmic form to be linear, but apparently with sticky ends, since Hsing-Jien Kung has found circles when the linear forms are spread in high salt. Incidentally, the references you cite for the "long minus-short plus" duplex are not really appropriate; we've described the structure in two papers in the May J. Virol., and Gianni, et al have done so in Nature last year. The only evidence other than yours for supercoiled DNA being confined to the nucleus is in our (joint) J. Mol. Biol. paper. In fact, our previous work is often misquoted (e.g., in David's Nobel lecture) as showing form I in the cytoplasm, and Weinberg's stuff never addresses the nucleus vs. cytoplasmic issue. Also, you would be doing me a personal favor by including Ram's Nature paper as the primary reference on supercoils; he is quite sensitive to the omission of this paper by many authors. I have received the proof of our J. Mol. Biol. paper; it should appear shortly (in Vol. 105).

Best regards,

Harold E. Varmus, M.D.
Associate Professor of Microbiology

HEV/es