



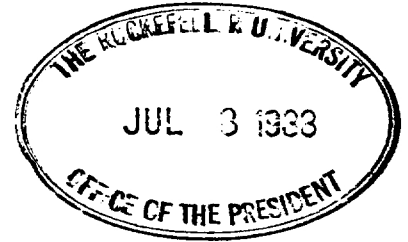
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 2, 1988

Dr. Joshua Lederberg
President
The Rockefeller University
New York, New York 10021-6399



Dear Josh:

Thank you for your note of May 17 and the article from Nature entitled "Activation of Human Immunodeficiency Virus Type 1 by DNA Damage in Human Cells." This elegant study of HIV promoter enhancement by Valerie et al. does indicate that HIV gene expression can be dramatically enhanced by agents that elicit a "stress response" in mammalian cells. You ask the important question of whether AZT could elicit a similar stress activation mechanism and thus, paradoxically, enhance HIV gene expression, replication, and clinical disease.

A protocol involving administration of AZT to asymptomatic HIV seropositive individuals has been in process for almost a year. In this study patients are monitored frequently; T4 cell numbers, antigen levels, and cultures are obtained at 4- to 8-week intervals. While the study is incomplete, enough patients have received AZT and placebo so that any rapid acceleration of the pace of disease or immunopathology would likely have been observed if a dramatic activation had occurred in vivo. The positive effects of AZT on ARC patients likewise argue against a deleterious clinical effect due to provirus activation.

Dr. Michael Norcross's laboratory has been actively involved in characterization of control mechanisms of HIV enhancer sequences using a CAT assay similar to that in the Rosenberg paper [Kaufman, J.D., Valendra, G., Rodriguez, G., Bushar, G., Giri, C. and Norcross, M.A. (1987) Phorbol Ester Enhances HIV Promoted Gene Expression and Acts Upon a Repeated 10 Base Pair Enhancer Element, *Mol. Cell. Biol.*, 7(10):3759-3766]. The capacity of AZT and other nucleotide analogs will be examined in a CAT expression system in HELA cells to ascertain whether there is any evidence for HIV transcriptional enhancement by AZT.

It was good to hear from you. I hope we can get together when you come to Washington.

Sincerely yours,

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs