STANFORD UNIVERSITY MEDICAL CENTER

DEPARTMENT OF GENETICS

December 7, 1976

COPY

FRIED, John

Dr. John Fried
Syntex Corporation
Stanford Industrial Park
Palo Alto, California 94304

Dear John,

I was interested and gratified to learn of the intense efforts you are making to apply simplified mutagenicity assays to the evaluation of the safety of Naproxen with respect to carcinogenesis.

These methods have been widely and properly acclaimed as offering a substantial increase in sensitivity, as well as mitigation of cost and time, over the whole animal methods generally used five years ago. The main use of methods like the Ames test is to furnish a cheap and sensitive first filter for screening suspect new compounds. For the categories of compounds like alkylating agents, or substances that are metabolized into alkylating agents, the test is probably far superior to animal testing - indeed is probably going to produce a measure of false positives from the standpoint of practical public health.

Unfortunately a certain number of carcinogenic substances like asbestos and sex hormones operate by very different mechanisms and will not be picked up by the Ames test. Plainly, animal tests must be continued for assaying such compounds. In fact, I am rather deeply concerned that the rote way in which animal testing is prescribed today makes them still quite inefficient for the job they are called upon to do.

I have not really been able to take the time to go into a close analysis of the Naproxen situation per se, and my remarks about the testing situation generally come from a broad (but then somewhat distant) perspective rather than from a close analysis of the data on the existing compounds. I have to say, however, that I am not much persuaded that there is any logic to connect the 22-month chronic toxicity study requirement, with the need to look at carcinogenic potential over still longer periods of time with larger numbers of animals. The former battery of tests are evidently designed to be able to detect only the most potent of carcinogens; and one can well argue that such agents are likely to be picked up equally well either by the microbial assays or by other evidences of cell-biological abnormalities. Compounds like anti-inflammatory agents that are intended to be used chronically, over long periods of time, and in contexts where there is some potentiality for patient abuse and imperfect medical supervision, would seem to me to warrant the most stringent long-term testing <u>regardless</u> of the outcome either of the 22-month chronic toxicity, the microbial assays, or one's favorable theoretical judgment based on the known biochemistry of the compound. I was then both pleased to learn that you have tests of this kind in progress <u>and</u> rather surprised and dismayed that the FDA had not required them at the time of initial registration either of Naproxin or of the other anti-inflammatory agents on the market at the present time. While there is nothing in the information you gave me to suggest any other than a favorable outcome of

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such further rigorous testing, I would hope that this could become the accepted standard, at least pending a further rationalization of cancer-testing procedures.

While it has been some time since I terminated my long association with the Molecular Biology Institute at Syntex, I recall those times with great affection and it was a pleasure to renew these acquaintanceships.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr